NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of No.292; Aripiprazole for the treatment of acute manic and mixed episodes in children with bipolar disorder

Original publication date:	July 2013
Review date	July 2017
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA292, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. We should consult on this proposal.

2. Rationale

The new evidence identified from the literature searches and registered trials does not indicate that a review of the recommendations in technology appraisal 292 is needed. In addition, the marketing authorisation has not changed and the original prices for aripiprazole used in TA292 are broadly in line with current prices. It is therefore proposed that technology appraisal guidance 292 is transferred to the 'static guidance list'

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology since the guidance was published?
The original prices for aripiprazole from BNF 63 are broadly in line with those in the current eBNF (April 2017, BNF 73). However, there are now generic versions of aripiprazole, which are listed as the same price or less in eBNF.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There has been no change to the marketing authorisation for aripiprazole since TA292 was published and none is anticipated.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
In TA292, the committee concluded that there remained uncertainty surrounding the subgroup analysis by age group. The committee heard that the licence for aripiprazole was restricted to adolescents aged 13 or older because of safety concerns in younger people. The Committee noted that there was no change in treatment effect between the age subgroups, however this subgroup analyses was uncertain as it was based on small numbers. The Committee concluded that evidence of treatment effect should be based on the whole trial population of NCT00110461. Findling et al reported results of a randomized, double-blind, 30-week, placebo-controlled study of aripiprazole in youths with bipolar I disorder (manic or mixed) with or without psychotic features. The results suggested that aripiprazole 10 mg/day and 30 mg/day were superior to placebo and generally well tolerated in pediatric subjects with bipolar I disorder up to 30 weeks. The study did not resolve any uncertainty surrounding the treatment affect between the age subgroups.
Additional comments
An FDA alert notes that aripiprazole is associated with uncontrollable urges for example compulsive urges (compulsive gambling, shopping, eating and sexual activity) which may results in harm to patients if not recognised.

The search strategy from the original ERG report was adapted and re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2013 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix C for further details of ongoing and unpublished studies.

4. Equalities issues

No equalities issue were identified in the original guidance.

GE paper sign off: **Meindert Boysen, 26 May 2017**

Contributors to this paper:

Information Specialist: Toni Shaw

Technical Analyst: Stuart Wood

Technical Adviser: Eleanor Donegan

Associate Director: Melinda Goodall

Project Manager: Samantha Shannon

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of aripiprazole, within its licensed indication, for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents.

6. Current guidance

Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older).

7. Research recommendations from original guidance

None

8. Cost information from original guidance

“Aripiprazole is available in 5 mg, 10 mg, 15 mg and 30 mg tablets, as 10 mg and 15 mg orodispersible tablets, and as an oral solution (1 mg/ml). The acquisition cost of aripiprazole 5 mg, 10 mg and 15 mg is £95.74 for 28 tablets. For 30 mg it is £191.47 for 28 tablets, and for oral solution it is £102.57 for 150 ml. Costs exclude VAT and are from the 'British national formulary' (BNF, edition 63). For people whose condition responds to aripiprazole, the expected length of a course of treatment is 12 weeks. For a course of 12 weeks (84 days), the 10 mg dose would cost £287.22. This cost would be the same for a 15 mg dose. A course of the 30 mg dose would cost £574.41. Costs may vary in different settings because of negotiated procurement discounts.”

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred (to a specified date)	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Confidential information has been removed.

Appendix C – other relevant information

1. Relevant Institute work

Published

Bipolar disorder: assessment and management (2014 updated 2016) NICE guideline CG185. *The next review is given as 2017*.

In progress

None.

Referred - QSs and CGs

None.

Suspended/terminated

None.

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Abilify Maintena (Otsuka) – is an intramuscular (IM) preparation of aripiprazole for maintenance in people with bipolar disorder who experience manic episodes or schizophrenia according to Specialist Pharmacy Service (SPS).The March 2017 New Medicines Newsletter from SPS says the IM formulation is phase III filed for adults and in phase III for children / adolescents. A Bristol-Myers Squibb phase III trial of Abilify in children (age 4-9) with symptoms of mania used a tablet formation, which is the formulation listed as in development for this indication in children. SPS also suggests a formulation of abilify is in development which is 'embedded with Proteus® ingestible sensor for treating schizophrenia but the [redacted]	SPS says 'Schizophrenia and bipolar disorder in *children and adolescents* (license extension)' and in phase III of development for this indication. [redacted]	No

3. Details of changes to the indications of the technology

Confidential information has been removed.

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
The price in the original appraisal is "…aripiprazole 5 mg, 10 mg and 15 mg is £95.74 for 28 tablets. For 30 mg it is £191.47 for 28 tablets, and for oral solution it is £102.57 for 150 ml." This was from BNF 63 and excludes VAT.	The indication is the same. The original prices for Abilify from BNF 63 are broadly in line with those in the current eBNF (April 2017, BNF 73) which says the following: 5 mg, 10 mg and 15 mg is £96.04 for 28 tablets. For 30 mg it is £192.08 for 28 tablets, and for oral solution it is £102.90 for 150 ml. However, there are now generic versions of aripiprazole, which are listed as the same price or less in eBNF. NICE has contacted 12 manufacturers in addition to Otsuka regarding this RPP.

4. Registered and unpublished trials

None.

5. Relevant services covered by NHS England specialised commissioning

None.

Appendix D – References

Findling Robert L, Correll Christoph U, Nyilas Margaretta, Forbes Robert A, McQuade Robert D, Jin Na, Ivanova Svetlana, Mankoski Raymond, Carson William H, and Carlson Gabrielle A. 2013. "Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study." *Bipolar disorders* 15(2):138-49.