NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA213; Aripiprazole for schizophrenia in people aged 15 to 17 years

This guidance was issued in January 2011.

The review date for this guidance is November 2013.

1. Recommendation

The guidance should be incorporated, verbatim, into the ongoing clinical guideline on the recognition and management of schizophrenia presenting up to 18 years of age. The technology appraisal guidance should be placed on the 'static guidance list' so that the technology appraisal remains extant alongside the guideline. This has the consequence of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.

That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost-effectiveness of aripiprazole within its licensed indication for the treatment of schizophrenia in people aged 15-17 years.

3. Current guidance

1.1. Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone.

1.2. People aged 15 to 17 years currently receiving aripiprazole for the treatment of schizophrenia who do not meet the criteria specified in 1.1 should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the person with schizophrenia, and if appropriate, their parents or carers.

4. Rationale[1]

This review proposal has been prepared ahead of the review date specified in the guidance because there is a related Clinical Guideline in development. In considering the options for this proposal the principles outlined in the Department of

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

Health policy document PWG IB (10)05 have been taken into account. The criteria for updating a technology appraisal in an ongoing guideline and a summary of options considered can be found in Appendix 1.

This guidance was published only recently (January 2011) and there have been no significant new developments in the evidence base to suggest that an update is necessary. Given the recentness of the guidance and noting that the extension of the marketing authorisation to include the treatment of schizophrenia in people aged 15 to 17 years was granted less than two years ago, it is not anticipated that this treatment will be established and embedded in the NHS. Spending on aripiprazole continues to rise (see Appendix 3 – note that the data are not linked to diagnosis and the age of the patient). Therefore the guidance does not meet the criteria for updating within a Clinical Guideline.

Consequently it is recommended that the technology appraisal guidance is incorporated, verbatim, into the clinical guideline. The Technology Appraisal guidance will be moved to the static list until the relevant Clinical Guideline is reviewed. This has the consequence of preserving the funding direction for the guidance.

5. Implications for other guidance producing programmes

The Clinical Guidelines programme has indicated that they do not object to this proposal. The intention to incorporate the Technology Appraisal into this Clinical Guideline was signalled in the draft scope, which was consulted on between 20 December 2010 and 17 January 2011.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from December 2009 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 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The initial UK marketing authorisation for aripiprazole was for the treatment of schizophrenia in adults. Subsequently an extension was sought to include the treatment of schizophrenia in adolescents aged 13 to 17 years. The Committee for Human Medicinal Products (CHMP) concluded that the proposed extension was approvable provided the population is restricted to people aged 15 years and older. The population considered in TA213 was people aged 15 to 17 years. This guidance was published in January 2011 and the wording of the marketing authorisation remains unchanged since then.

No new evidence on the use of aripiprazole in people aged 15 to 17 years for the treatment of schizophrenia has been published since TA213 was issued. Although two studies relating to the use of aripiprazole have recently been published, these relate to data that had already been made available to the Appraisal Committee

during the development of TA213 and are not expected to change the current recommendations.

The price of aripiprazole has remained constant since TA213 was published. The price of the comparator treatments have changed slightly: for olanzapine from £79.45 to £87.46 per pack and for clozapine, from £24.64 to £21.56 per pack.

A clinical guideline on the recognition and management of schizophrenia presenting up to the age of 18 years was referred to NICE by the Department of Health in February 2010. The scope for this guideline states that it will cover the use of all antipsychotics licensed for the treatment of schizophrenia in the UK for young people and will provide recommendations on treatment options when an antipsychotic medication is ineffective and/or not tolerated. It is clear that the recommendations on the use of aripiprazole for people aged 15 to 17 years with schizophrenia in TA213 fall within the remit of this clinical guideline. In view of this, and considering that no new evidence for aripiprazole has been published since TA213 was issued, it is recommended that TA213 should be incorporated into the ongoing clinical guideline and transferred to the 'static guidance list'.

8. Implementation

A submission from the Implementation team is attached at the end of this paper (see Appendix 3).

9. Equality issues

During the development of TA213, consultees and commentators suggested that one area of potential discrimination was that the diagnosis of schizophrenia requires a definitive methodological approach using precise diagnostic criteria which may not be met by people with learning difficulties. The Committee concluded that there are not sufficient data to provide evidence on how the clinical and cost effectiveness of aripiprazole may differ for people with schizophrenia who have learning difficulties.

There are variations in the way different ethnic groups access and use specialist mental health services. Therefore it is likely that there will be important differences between ethnic groups in children and young people with schizophrenia. Moreover, the incidence of psychosis varies with ethnic group, locality, social disorganisation and poverty. The ongoing clinical guideline will include specific consideration of the needs of children and young people from black and minority ethnic groups.

GE paper sign off: Janet Robertson, 26 April 2011

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Appendix 1 – 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.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	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.	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.	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 the on-going clinical guideline on the recognition and management of schizophrenia presenting up to 18yrs of age.	**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.**	**Yes**
The guidance should be updated in an on-going clinical guideline.	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

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list' until the ongoing clinical guideline is considered for review.	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

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Core interventions in the treatment and management of schizophrenia in primary and secondary care (update). Clinical Guideline CG82. Issued: March 2009. Review date: March 2012. Note that this guideline covers adults (aged 18 and over). It does not specifically look at younger people other than those who are receiving treatment from early intervention services.

Antenatal and postnatal mental health: clinical management and service guidance. Issued: February 2007. Review date: February 2012.

The clinical effectiveness and cost effectiveness of electroconvulsive Therapy (ECT) for depressive illness, schizophrenia, catatonia and mania. Technology Appraisal TA59. Issued April 2003. Review date: TBC.

In progress

Schizophrenia: recognition and management of schizophrenia presenting up to 18 years of age. Clinical Guideline. Publication date: TBC.

Proposed technology appraisal

Loxapine inhalation for the rapid treatment of agitation in patients with schizophrenia or bipolar disorder. Note, this topic is currently being considered through the scoping process and has not yet been formally referred for appraisal.

Details of changes to the indications of the technology

Indication considered in original appraisal	**Proposed indication (for this appraisal)**
Treatment of schizophrenia in people aged 15 -17 years. Note that the full licence for aripiprazole allows its use in patients aged 15 years and older. This TA arose as a result of a specific licence extension to include the adolescent population (15–17yrs). See 'additional information' section for further details.	Treatment of schizophrenia in people aged 15 -17 years.

Details of new products – all currently being studied in adult populations only

Drug (manufacturer)	Details (phase of development, expected launch date,)
Aripiprazole depot injection (Otsuka)	Phase III.
Asenapine (Merck)	CHMP negative opinion, June 2010.
Loxapine inhalation (Alexza Pharmaceuticals)	For agitated patients with schizophrenia or bipolar disorder. Phase III. EU filing anticipated mid-2011.
Lurasidone (Dainippon)	Phase III.
LY 2140023 (Eli Lilly)	Phase III.
Paliperidone (Janssen-Cilag)	Phase III in patients aged 12-17yrs.
Paliperidone palmitate (Janssen-Cilag)	Long acting injectable formulation. CHMP positive opinion in December 2010.
RG1678 (Roche Products)	Phase III. Regulatory filings planned for 2013.
Zicronapine (Lundbeck)	Phase II. UK launch planned Q4 2012.

Registered and unpublished trials

Trial name and registration number	Details
A Long-Term Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aripiprazole (OPC 14597) as Maintenance Treatment in Adolescent Patients With Schizophrenia. NCT01149655; 31-09-266.	Not yet open for recruitment Estimated completion date: June 2014 Participants aged 13 – 17 years n = 340
Safety and Tolerability of Aripiprazole in Adolescents With Schizophrenia or Children and Adolescents With Bipolar I Disorder, Manic or Mixed Episode With or Without Psychotic Features. ATTAIN 267; NCT01122927; 31-09-267.	Currently recruiting Estimated completion date: November 2015 Participants aged 10 - 17 years n = 463

Trial name and registration number	Details
Comparison of Aripiprazole and Risperidone for the Treatment of People With First-Episode Psychosis. NCT00320671; R01 MH060004-02; DSIR 83-ATAP.	Currently recruiting Estimated completion date: July 2011 Participants aged 15 - 40 years. n = 242
Effectiveness and Safety of Flexible Doses of Paliperidone Prolonged Release in Adolescent Patients With Schizophrenia. NCT01009047; CR016675; R076477PSZ3003.	Currently recruiting Estimated completion date: November 2011 Participants aged 12 -17 years n = 228
Tolerance and Effect of Antipsychotics in Children and Adolescents With Psychosis. NCT01119014; TEAprotocolversion5-11 03 2010; 2009-016715-38.	Currently recruiting Estimated primary completion date: August 2012 Participants aged 12 -17 years n = 300

Additional information

An injectable formulation of aripiprazole is available for rapid control of agitation and disturbed behaviours in patients with schizophrenia when oral therapy is not appropriate. The SPC recommends that treatment with the injectable aripiprazole solution should be discontinued as soon as clinically appropriate.

Appendix 3: Implementation Submission

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION PROGRAMME

Guidance Executive Review

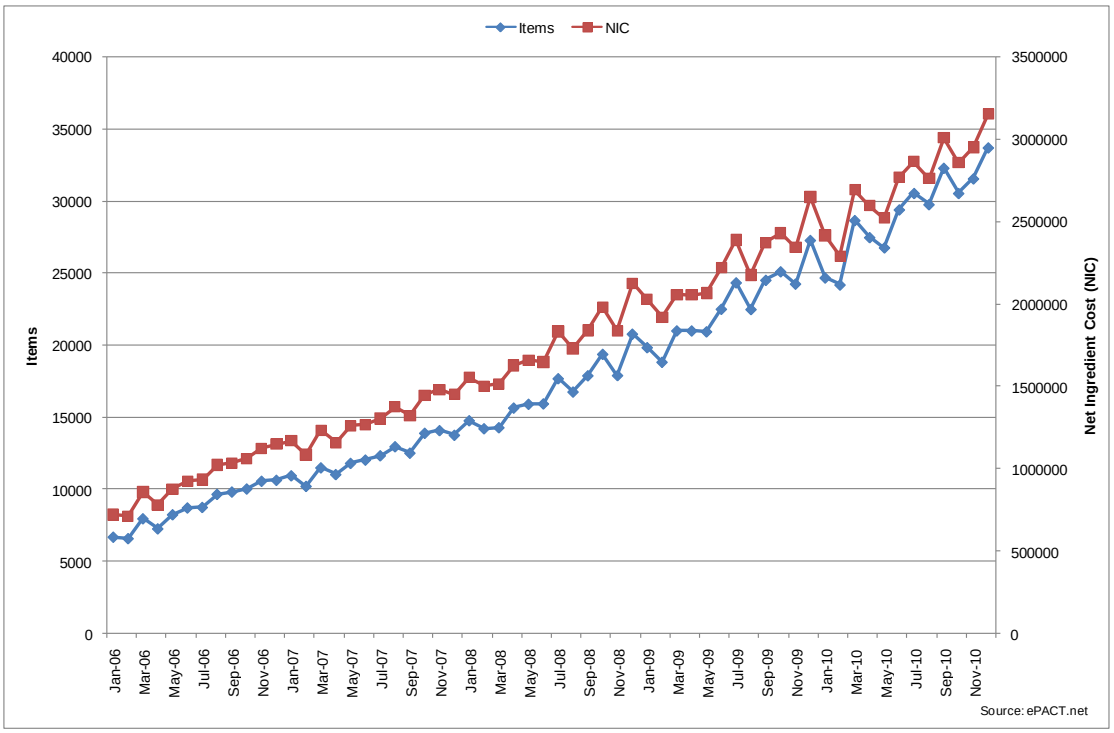
Technology appraisal TA213: Aripiprazole for schizophrenia in people aged 15 to 17 years

1. Routine healthcare activity data -

This section provides information on cost and volume for aripiprazole prescribed and dispensed in primary care in England using data obtained from the electronic Prescribing Analysis and Cost Tool (ePACT) system. All costs stated in this report are based on Net Ingredient Cost (NIC).

1.1 Primary care prescribing (ePACT) - Aripiprazole

Figure 1 Trend in the cost and volume of prescribing aripiprazole in primary care in England



The above chart shows that the prescribing costs and volume for aripiprazole has increased over time. By December 2010 the Net Ingredient Cost was £3,151,705 (33,701 items).

This data must be interpreted with caution as data are not linked to diagnosis and the age of the patient. It is therefore not possible to ascertain what proportion of prescribing relates to patients with schizophrenia and the age of the patient. Also due to limitations in the availability of data the most recent dataset is up to December 2010. As the technology appraisal was published in January 2011 it is not possible to comment on the uptake of aripiprazole post publication, the data is purely retrospective.

Notes:

- The electronic prescribing analysis and cost tool (ePACT) system covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Pricing Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions written in hospitals but dispensed in the community (FP10 [HP]) are not included in PACT data. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

- Volume: The basic measure of volume in PACT data is the number of prescription items which refer to a single item on a prescription form.

- Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

- Ideally data would show the total number of patients prescribed a medicine and the volume and duration of treatment. However, the current datasets do not facilitate this type of analysis. Cost and volume therefore need to be considered together to provide the closest approximation. Cost provides a more accurate view of the total amount of a medicine dispensed. However, it does not provide an indication of the number of patients prescribed a medicine. Volume therefore provides an indication of the number of items, although it does not account for patients receiving different dosages or durations.

- Unfortunately this data does not link to diagnosis or age so needs to be treated cautiously in relation to the specific recommendations of the guidance.

There are currently no relevant publications on the Uptake Database (ERNIE).