National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents

Response to consultee and commentator comments on the remit and draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background	Bristol Myers Squibb and Otsuka Pharmaceuticals	None	No action required
	Department of Health	Our only question is whether this is timely or premature, given that according to the scoping paper the study to define its effectiveness or otherwise is currently underway? Would it not be better to wait for the study to report its findings?	Comment noted. The scheduling of appraisals is generally determined by the expected marketing authorisation timings.
The technology/ intervention	Bristol Myers Squibb and Otsuka Pharmaceuticals	None	No action required
Population	British Association for Psychopharmacology	It may be appropriate to consider pre and post pubertal.	Comment noted. The scope has been updated to include assessment by pre and post pubescent subgroups if the evidence allows.

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	Bristol Myers Squibb and Otsuka Pharmaceuticals	We expect that differences in aripiprazole's effectiveness may be observed in subgroups containing patients in different age groups (e.g., younger compared with older children/adolescents).	Comment noted. The scope has been updated to include assessment by pre and post pubescent subgroups if the evidence allows.
Comparators	British Association for Psychopharmacology	I think these are correct	Comment noted. No action required
	Bristol Myers Squibb and Otsuka Pharmaceuticals NHS Warwickshire	The most relevant comparators have been listed and are routinely used in day-to-day clinical practice. Of the listed comparators, only lithium is licensed in this age group.	Comment noted.
Outcomes	Bristol Myers Squibb and Otsuka Pharmaceuticals	None	No action required
	Royal College of Paediatrics and Child Health	Need to use body/mass index	Comment noted. The outcomes in the draft scope have been amended to include body mass index (adjusted for the child's age and gender).
Economic analysis	Bristol Myers Squibb and Otsuka Pharmaceuticals	None.	No action required

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Equality and Diversity	Bristol Myers Squibb and Otsuka Pharmaceuticals	None	No action required
Other consideration	Bristol Myers Squibb and Otsuka Pharmaceuticals	None	No action required
Questions for consultation	British Association for Psychopharmacology	Should aripiprazole be specified as a monotherapy only or will it also be used as an adjunct to other treatments? **Should be considered as monotherapy and also in conjunction with lithium and valproate**	Comment noted. The draft scope has been amended to include consideration of the effectiveness of aripiprazole alone or in combination with lithium or valproate, if the evidence allows.
	British Association for Psychopharmacology	Does treatment differ according to whether the episode is defined as 'manic' or 'mixed'? **Not at present due to lack of evidence.**	Comment noted.
	British Association for Psychopharmacology	Is it anticipated that aripiprazole will be licensed for the prevention of acute episodes? If not, is it appropriate to retain 'recurrence of manic episodes' in the list of outcomes? **Yes**	Comment noted.

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	British Association for Psychopharmacology	At the scoping workshop it was suggested that weight gain or loss be included in the list of outcome measures. How should this outcome be interpreted given that for the population in the scope, it is expected that increases in height will be associated with changes in weight? **Should use z scores and include bmi z scores also**	Comment noted. The outcomes in the draft scope have been amended to include body mass index (adjusted for the child's age and gender).
	British Association for Psychopharmacology	Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of patients in whom aripiprazole is expected to be more clinically effective and cost effective or other groups that should be examined separately? **None where would think it would be more important but maybe the controversial group with bpd and adhd (in whom true bpd is rather unlikely) may be poor responders**	Comment noted.
	British Association for Psychopharmacology	Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality? **Not that i am aware of**	Comment noted. No action required
	British Association for Psychopharmacology	Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Not really apart from lower potential for hyperprolactinaemia**	Comment noted.

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	British Association for Psychopharmacology	Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Not really**	Comment noted. No action required
	British Association for Psychopharmacology	Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits **I can't access this just now**	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Should aripiprazole be specified as a monotherapy only or will it also be used as an adjunct to other treatments?** The use of aripiprazole will depend on the license that is granted by the European Medicines Agency. It is expected that aripiprazole will be specified as a monotherapy, in line with the pivotal clinical trial.[1] However it is possible that aripiprazole will be used in combination with agents of other classes, including mood stabiisers.	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Is the population defined appropriately? Should the population be defined more precisely by age?** The pivotal Phase III trial[1] included patients aged ≥10 years, and this is expected to be reflected in the licence, although this may specify an older population (e.g., aged >=13 years).	Comment noted.

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	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Have the most appropriate comparators for the treatment of acute manic and mixed episodes in bipolar disorder in children and adolescents been included in the scope? Are the comparators listed routinely used in clinical practice?** The most relevant comparators have been listed and are routinely used in day-to-day clinical practice, although, of the comparators, only lithium is licensed in this age group.	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Does treatment differ according to whether the episode is defined as 'manic' or 'mixed'?** In general, treatment does not differ between manic and mixed episodes.	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Is it anticipated that aripiprazole will be licensed for the prevention of acute episodes? If not, is it appropriate to retain 'recurrence of manic episodes' in the list of outcomes?** Aripiprazole is not expected to be licensed for the prevention of acute manic episodes. Although no antipsychotics are licensed for the prevention of manic episodes, in clinical practice these therapies are routinely used in patients in the post-acute phase to prevent recurrence of manic episodes.	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**At the scoping workshop it was suggested that weight gain or loss be included in the list of outcome measures. How should this outcome be interpreted given that for the population in the scope, it is expected that increases in height will be associated with changes in weight?** Appropriate statistical analyses will be conducted to control for the gender-specific influence of height over weight (e.g., Z-scores)	Comment noted. Outcomes in the draft scope have been amended to include body mass index (adjusted for the child's age and gender).

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	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of patients in whom aripiprazole is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Yes – appropriate subgroups have been specified. We expect that differences in aripiprazole's effectiveness may be observed in subgroups containing patients in different age groups.	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?** No.	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Aripiprazole will be the first antipsychotic to be licensed in this age group, and so presents physicians with a licensed alternative to the off-licence treatment options currently available.	Comment noted.
	Bristol Myers Squibb and Otsuka Pharmaceuticals	**Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** The quality of life and productivity of caregivers[2] is of vital importance to young patients with bipolar disorder and is very unlikely to be captured in existing QALY methodology.	Comment noted.
Additional comments on the draft	Bristol Myers Squibb and Otsuka Pharmaceuticals	No further comments	No action required

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scope	Royal College of Nursing	With regards to the diagnosis of bipolar disorder in children, we consider that extreme caution needs to be used in making a lifelong defined diagnosis in developing children and adolescents. If it is a given that one treats the symptoms and not diagnosis then it would not be useful to aim specific medication at phase specific illness episodes of bipolar disorder. It is acknowledged that in some children severe and obvious mood episodes may require targeted pharmacological interventions but even then there is a tendency to avoid labelling children with a life long illness. One would exercise caution and not use the same illness models for adults and children so as to discourage what could lead to unnecessary labelling of children	Comment noted. The diagnosis of bipolar disorder in children is outside the remit of this scope.

The following consultees/commentators indicated that they had no comments on the draft scope

GlaxoSmithKline
Royal College of Pathologists
Welsh Government