Ipswich and East Suffolk Clinical Commissioning Group

New Medicine Report	**Aripiprazole (Adopted by the CCG until review and further notice)**
Document Status	Agreed by Suffolk D&TC
Traffic Light Decision	**RED Hospital Consultants only**
Date of Last Revision	12th January 2004
Approved Name	Aripiprazole
Trade Name	Abilify (™ in USA)
Manufacturer	Bristol-Myers Squibb in collaboration with Otsuka Pharmaceutical Co.
Legal Status	POM – awaiting licence submitted December 2001
Indication	Treatment of Schizophrenia
Dosage	10mg to 30mg daily
Cost	Not known - similar products are about £100 per month
Possible Number of Suffolk Patients	1 in 1,000 are at risk of at least one episode
Number Needed to Treat	Not calculated
Treatment Alternatives	Current “typical” & “atypical” antipsychotics
Future Alternatives	Not known
Possible Future Indications	Acute bipolar disease Psychosis in Alzheimer’s Disease

Reviewer’s Comments

The symptoms of schizophrenia have long been treated with the older antipsychotics with their many and varied side effects which often cause the patient to withdraw from treatment. In addition the older drugs tend to have little influence on the more negative symptoms. Newer “atypical” antipsychotics are less likely to produce a number of the unwanted side effects, however they do seem to produce weight gain and QT prolongation.

The development of aripiprazole, a dopamine-serotonin system stabiliser, which acts in a different way may help to eliminate some of these side effects which lead to non-compliance. However it is not yet clear whether this different mode of action will have any real clinical benefit over current treatments in the longer term.

From the data available it would seem that aripiprazole is more effective than placebo and at least as effective as haloperidol and risperidone at treating

schizophrenia. However there is no clear evidence that this product is a major advance in treatment.

Long-term use will be required to confirm both the efficacy of the product and the accuracy of the current safety data.

No information is available to support the use of aripiprazole in the treatment of refractive patients thus accurate assessment will be important in ensuring the product is used in suitable patients.

Evidence Reviewed

Paper, Review, Abstract etc.	Level of evidence
Information, posters and abstracts provided by BMS	IV
Bowles TM, Levin GM. Aripiprazole a new atypical; antipsychotic drug. Ann Pharmacother 2003;37:687-94	I
Crismon ML, DeLeon A, Miller Al. Aripiprazole does partial dopaminergic agonism translate into clinical benefits? Ann Pharmacother 2003;37:738-40	I
Cada DJ, Levien T, Baker DE. Formulary drug review Aripiprazole Hosp.Pharm 2003;38(3) 247-256	III
Public Citizen's eLetter The new anti-psychotic drug aripiprazole. April 2003 www.citizen.org/letter/articles/abilify.htm	IV
FDA approval letters etc for the product www.fda.gov/cder/foi/nda/2002/21-436_Abilify.htm	III

Level of evidence adapted from "Quick and Clean" : authorative health technology assessment for local health care contracting Andrew Stevens, Duncan Collin-Jones & John Gabbay Health Trends Vol 27 No 2 1995

Review

Schizophrenia is a major cause of morbidity. A psychotic disorder, it is characterised by disturbances in the form and content of thought, mood, sense of self and relationship to the external world. It causes severe impairment of social functioning and normally starts in the mid teens.

Traditional antipsychotics have a tendency to improve only the positive symptoms such as delusions, hallucinations and thought disorder with little or no effect on the negative symptoms such as the inability to express emotion and withdrawal. It is estimated that 30% of all patients will fail to respond to therapy and up to 50% only partially respond.[i] This class of medication also tends to induce extrapyramidal symptoms (EPS) such as parkinson-like symptoms and akathisia in use, which is a drawback to treatment, leads to

lack of compliance and the need to take additional medication to combat these symptoms.
Atypical agents have been introduced which seem to have less risk at lower doses of inducing EPS. They are however often characterised by significant weight gain that leads to non-compliance with therapy.

Aripiprazole is a new "atypical" antipsychotic which the makers claim is the next generation with a unique mechanism of action believed to act as a dopamine-serotonin system stabiliser. It is suggested that it preserves or enhances dopaminergic activity where it is too low and reduces the activity where it is too high. The true clinical outcome of this claim has yet to be confirmed.

A number of scales have been used to assess the efficacy of the medication including:
Brief Psychiatric Rating Scales (BPRS) which consists of 18 items to be scored. A decrease in the overall score reflects an improvement.
Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I). The CGI-S is a single rating of how ill the rater feels the subject is. A decrease in the CGI-S score reflects an improvement. The CGI-I is a single rating of how the rater feels the subject has improved from the baseline assessment. An increase reflects the rater's view of the improvement in the subject.
Positive and Negative Syndrome Scale (PANSS). The positive subscale rates the seven positive symptoms of schizophrenia. Similarly the negative subscale rates the seven negative symptoms of schizophrenia. An improvement in the positive, negative or total score is seen when the patient improves relative to their starting point.

No full trial papers have been supplied by BMS, rather abstracts and extracts were the basis of the information provided.

Kane investigated 414 patients with a diagnosis of schizophrenia or schizoaffective disorder with relapse in a 4 week trial. Patients were treated with either a placebo, haloperidol, aripiprazole 15mg or 30mg each taken daily. Only 248 patients completed the trial. All treatments were more effective than placebo in improving outcomes.

Saha reported a trial which compared aripiprazole with risperidone in 404 hospitalised patients over a period of 4 weeks. All treatment arms were more effective than placebo. It is stated that aripiprazole demonstrated activity in respect of both positive and negative symptoms by the end of week 1 whereas risperidone showed activity in respect of positive symptoms at week one and negative symptoms at the end of week 2. The full clinical impact of this is difficult to ascertain from the limited information available.

Two long-term trials are reported.

Carson investigated the prevention of relapse in a 26 week study which enrolled 310 patients equally divided to aripiprazole 15mg or placebo. In the treatment group 34% relapsed compared to 57% in the placebo group (P<0.001).

Kujawa evaluated the duration of response in 1294 patients who started treatment following an acute exacerbation and continued treatment over a period of 52 weeks. Patients were randomised to aripiprazole 30mg (n=861) or haloperidol 10mg daily (n=433) on a 2:1 ratio. A once only reduction to 20mg aripiprazole or 7mg haloperidol was allowed for tolerability. At week 52 only 43% of the patients in the aripiprazole arm and 30% of the patients in the haloperidol arm remained in treatment. More aripiprazole treated patients were maintained as responders at week 52 than those treated with haloperiodol (p≤0.001).

The FDA note that in each of the three positive fixed dose studies the lowest dose was numerically superior to all the higher doses. They have asked the company to carry out further research to investigate the optimal dose. It should be remembered that the side effect profile, as with most medication, worsens as the dose increases and clinicians should be particularly mindful of this when considering increasing the dose to elicit an improved response.

Adverse Effects etc.

For full information please refer to the Summary of Product Characteristics.

Aripiprazole is metabolised through CYP3A4 and CYP2D6 enzyme systems. Thus agents such as carbamazepine which induce CYP3A4 could cause an increase in metabolism and a reduction of plasma levels. Similarly agents such as fluoxetine and paroxetine which inhibit CYP2D6 or ketoconazole which inhibits CYP3A4 can inhibit elimination and cause increased blood levels.

The company notes in its information that aripiprazole shows a favourable safety and tolerability profile with low potential for extra-pyramidal symptoms, significant weight gain, prolactin elevation, cholesterol elevation, QT prolongation or sedation. The most common side effects are headache, agitation, anxiety, insomnia, dyspepsia, nausea, vomiting, light-headedness, somnolence, constipation, and akathisia.

It should be noted that in a 52 week trial patients with a BMI>27 experienced mean weight loss of 1.23kg but those with a BMI<23 experienced a minimum weight gain of 2.6kg (NB note the use of the word minimum, although from the

accompanying graph it might be interpreted that the mean weight gain is 2.6kg)

It is of concern to note that within the study period for the new product two possible cases of Neuroleptic Malignant Syndrome are noted in the USA data sheet. Given the low number of patients in the pre-marketing clinical trials (aprox 5,600) this seems rather high and it will be interesting to find the true rate when more patients are treated.

The Public Citizen Group note that in a particular type of rats aripiprazole caused retinal degeneration. The FDA has asked for further tests on different types of rat to be carried out post-authorisation. The clinical relevance of this problem in humans is not yet fully understood.

Health Economics

The total cost of treating schizophrenia in the UK was estimated in 1994 as £397 million[ii], (or 1.6 % of the then total health budget) of which drugs account for 5%. There are further losses to the community in indirect costs which have been estimated at £1.7 billion. The cost of drugs will have increased since then given the introduction of atypicals. It is not clear by how much the cost of hospitalisation will have fallen, if at all.

Prudo & Blum (1987) classified several groups of schizophrenic patients:-

Group 1	only a single episode with an average duration of 22 weeks
Group 2	episodes of a major disorder lasting up to 1 year
Group 3	episodes for 1-2.5 years
Group 4a	episodes of more than 2.5 years requiring predominantly community based care
Group 4b	episodes of more than 2.5 years requiring long-term care either in a hospital or intensive community programme

The total lifetime direct treatment costs for a one year incidence cohort were £390 million ranging from £3 million for group 1 to £309 million for group 4b. It was calculated that 97% of the total lifetime direct treatment costs were incurred by those in groups 4a and 4b who constitute less than 50% of a one year cohort. A sensitivity analysis thus shows that if patients can be moved down the groupings or prevented from moving up the groupings then the major cost savings will be found in the reduction of the numbers in groups 4a and 4b.

Given the expected number of the population who will experience one or more episodes of schizophrenia Table 1 can be constructed.

Table 1
To show the number of people expected to experience one or more episodes of schizophrenia.

PCT	Population	Expected number of patients at 1/1,000
Central	96,000	96
Ipswich	143,000	143
Suffolk Coastal	99,000	99
Suffolk West	203,000	203
Waveney	114,000	114
Total for Suffolk	655.000	655
Total for East Commissioning	338,000	338

Not all of these will require long-term treatment and it is difficult, with the limited amount of information available, to estimate the number of patients who will be prescribed this new product in preference to one of the older products. It is possible that there will be little effect on the budget if the correct sections of patients are currently receiving treatment with atypicals.

SUFFOLK DRUG AND THERAPEUTICS COMMITTEE

www.sphn.nhs.uk

New Drug Bulletin

Aripiprazole (Abilify ™)

SUFFOLK DRUG AND THERAPEUTICS COMMITTEE RECOMMENDATION:

Suffolk Drug and Therapeutics Committee has considered aripiprazole for the treatment of schizophrenia. It noted that aripiprazole is no more effective than existing treatments, but may have a lower potential for side effects in some patients. It therefore classifed aripiprazole as a "Red" drug (hospital only) in order that its side effect profile can be assessed - if data are presented showing that it has fewer side effects than existing agents its status can be reviewed.

FURTHER DETAILS

Licensed indication:	Treatment of Schizophrenia
Dosage:	10mg to 30mg daily
Cost:	Not known - similar products are about £100 per month
Number needed to treat	Not calculated
Treatment alternatives	Current “typical” & “atypical” antipsychotics

PRESCRIBING COMMENTS FROM THE SUFFOLK DRUG AND THERAPEUTICS COMMITTEE:

- The drug is no more effective than existing agents
- There are concerns about the incidence of neuroleptic malignant syndrome
- Reduced incidence of weight gain may be an advantage in selected patients
- Local consultants commented that the interest in the drug was due to its potentially favourable side effect profile, and that it should be prescribed by consultants initially.

Aripiprazole carries a black triangle in common with all new drugs. All suspected adverse reactions should be reported to the CSM on a yellow card.

Paul Berry
Prescribing Medical Advisor
January 2004