7.1 ARIPIPRAZOLE, tablets, 10 mg, 15 mg, 20 mg, 30 mg, Abilify® – Bristol-Myers Squibb Australia Pty Ltd

Purpose of Application:
Authority required listing for schizophrenia.

Registration Status:
Aripiprazole was registered on 21 May 2003 for the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy.

Mechanism of Action:
Aripiprazole is a novel antipsychotic. Its mechanism of action is unknown, however it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at dopamine D_2 and serotonin $5HT_{1A}$ receptors and antagonist activity at serotonin $5HT_2$ receptors.

Dosage:
The recommended starting and maintenance dose of aripiprazole is 15mg/day administered as a single daily dose without regard to meals. Doses in the range 15-30mg have been effective in clinical trials. Daily dosage may be adjusted on the basis of individual clinical status with the range of 15-30mg daily. There is no evidence that doses higher than 15 mg/day are more effective.

No dosage adjustment is required in patients with renal or hepatic (Child-Pugh Class A, B or C) impairment or in patients ≥ 65 years of age. The safety and effectiveness of aripiprazole in patients under 18 years of age has not been established.

Background:
An application for aripiprazole was rejected by the PBAC at its June 2003 meeting. The PBAC rejected the submission because the evidence supporting the claim of equi-effectiveness with olanzapine was inconclusive and the resulting cost-effectiveness claim was inadequately supported.

The PBAC noted that virtually all the trends in the measures of effectiveness in terms of schizophrenia across both head-to-head randomised trials favoured olanzapine over aripiprazole and some these were statistically significant. Thus, there was substantial doubt the submission's claims as to whether aripiprazole was as effective as olanzapine.
{See the June 2003 PBAC Minutes at item 5.5 for full details}

Comparator:
As previously, the comparator was olanzapine, which was accepted as appropriate by the PBAC at the June 2003 meeting.

Summary of Submission and Findings:
Scientific basis of comparison:
7.1.1 The table below summarises the key differences between the previous submission and the re-submission.

Key differences between the previous submission and the re-submission

	Previous submission	Re-submission
Therapeutic relativity	•aripiprazole has similar effectiveness to olanzapine with less toxicity	•aripiprazole is no worse than olanzapine in terms of effectiveness and safety, with a different clinical profile
Requested price	•10mg 30 tablets [redacted] •15mg 30 tablets •20mg 30 tablets •30mg 30 tablets	•10mg 30 tablets [redacted] •15mg 30 tablets •20mg 30 tablets •30mg 30 tablets
Clinical evidence	•one pivotal head-to-head trial (CN-138-002) •one supportive head-to-head trial (31-98-213) •one supportive open-label switching study (31-98-215)	•CN-138-002; 31-98-213; 31-98-215 •sub-set analysis of CN-138-002 •indirect comparison of aripiprazole and olanzapine using haloperidol as common comparator •AXIS questionnaire •BETA study
Economic model	•cost effectiveness using a risk prediction model and a decision tree model for costs	•cost-minimisation
Financial implications	•four different pricing scenarios	•five different pricing estimates

Comparative Effectiveness:

7.1.2 The ESC advised that the primary outcome measure in the key aripiprazole trial was weight gain rather than any measure of comparative effectiveness in schizophrenia.

7.1.3 New supportive data were presented in the re-submission. This included a sub-group analysis of the key trial, CN-138-002, in which only patients on doses of ≤20mg/day of aripiprazole and ≤15mg/day of olanzapine, were included in the analysis; an indirect comparison between aripiprazole, olanzapine and haloperidol; evidence from a randomised, open-label trial of aripiprazole (BETA); and evidence from the Australian AXIS program. The tables below summarise the results of the new data presented in the re-submission.

Summary of sub-set analyses of CN-138-002

[redacted]

7.1.4 From the results of the sub-group analyses of CN-138-002, the re-submission concluded that efficacy trends favour aripiprazole for PANSS Total, PANSS Negative, CGI-S and CGI-I, while improvement in MADRS total score favour olanzapine and PANSS positive results were similar. The re-submission claimed that the results were consistent with the claim that at doses that would be expected in clinical practice, aripiprazole was no worse than olanzapine in terms of clinical effectiveness. The ESC advised that this *post hoc* sub-group analysis included only [redacted] patients treated with aripiprazole and [redacted] treated with olanzapine at Week 26, there were no statistically significant differences between the groups, and thus the results should be interpreted with caution.

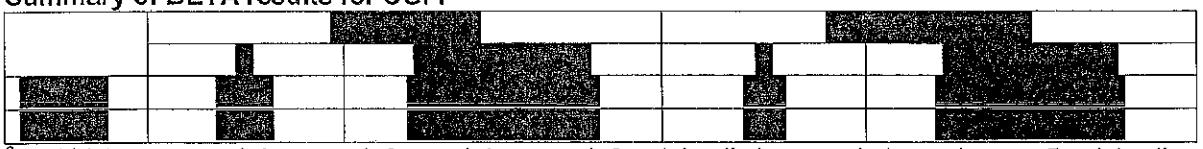
Summary of indirect comparison versus haloperidol

Efficacy endpoint	31-98-217/304		Tollefson et al (1997) – extension phase Week 7-52.	
	ARI[a]	HAL[a]	HAL	OLA
Mean change in PANSS Total Score	[redacted]	[redacted]	-21.0[b]	-24.2[b]
Mean change in PANSS Positive Subscale Score	[redacted]	[redacted]	-6.5[d] -6.2[b]	-7.5[d] -6.6[b]
Mean change in PANSS Negative Subscale Score	[redacted]	[redacted]	-6.8[d] -4.6[b]	-7.2[d] -6.2*[b]
Mean change in MADRS Raw Score (% mean change in MADRS Score)	[redacted]	[redacted]	~-11.0%[c]	~-8.5%[c]

* p<0.05 compared to HAL; [a] 31-98-217/304; [b] Revicki 1999 - reported the results of a sample of patients from the extension phase of the Tollefson 97 study; [c] Tollefson 1998 - reported the results from the extension phase of the Tollefson 97 study; [d] Hamilton 2000 - reported the results of a sample of European patients (n=778) from the extension phase of the Tollefson 97 study

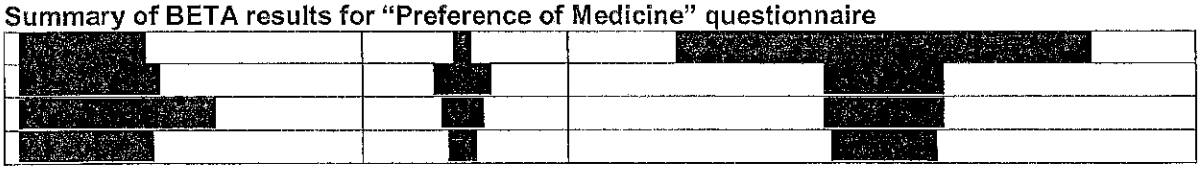
The indirect comparison was based on two trials, 31-98-217/304, which compared aripiprazole and haloperidol, and Tollefson et al 1997, which compared olanzapine and haloperidol. There was a statistically significant advantage for aripiprazole versus haloperidol in the treatment of negative and depressive symptoms of schizophrenia and a statistically significant advantage for olanzapine versus haloperidol for negative symptoms of schizophrenia. The comparison of olanzapine and haloperidol utilised the results from the extension phase of one study (Tollefson 1997) that were reported for different measures and sub-groups in three different papers. For example, Revicki 1999 reports the results of all patients who entered the extension phase, whereas Hamilton 2000 reports the results of a sample which included only European patients. The PES Commentary noted that caution should be taken in interpreting these results, as they come from different populations and as such may not be fully comparable.

Summary of BETA results for CGI-I [a]



[a] CGI-I 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse

Summary of BETA results for "Preference of Medicine" questionnaire

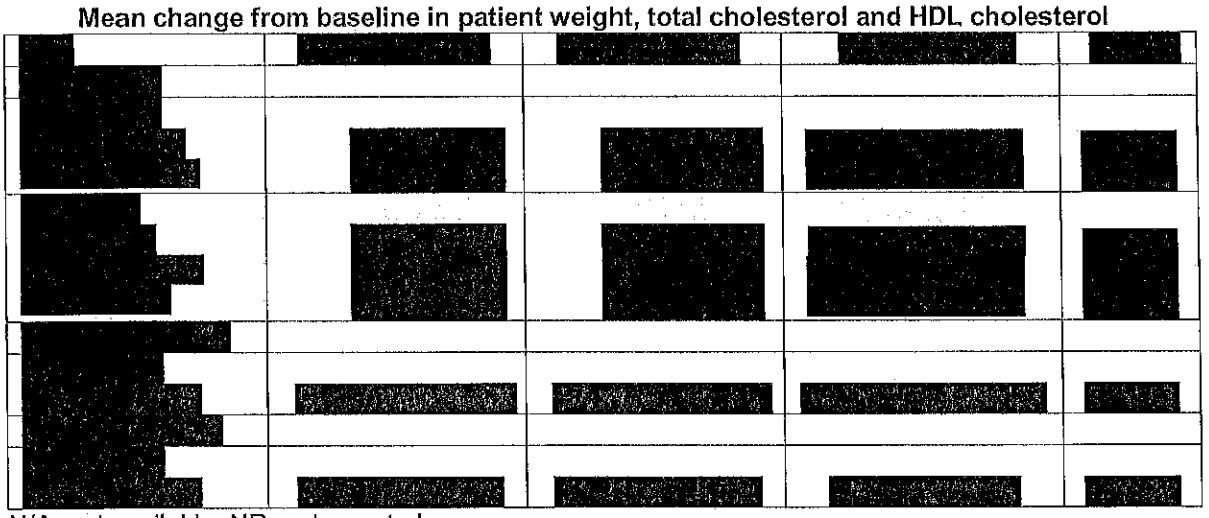


7.1.6 The BETA study was designed to assess the overall effectiveness of aripiprazole for the treatment of schizophrenia or schizoaffective disorder in a general psychiatric setting and to determine patients' medication preference compared with prior treatment. The re-submission stated that aripiprazole-treated patients demonstrated greater improvement in CGI-I compared to patients treated with 'standard of care'. Patients were also asked to rate their preference of medicine. The re-submission interpreted these results as "the patients felt "much better" or "slightly better" on aripiprazole than did patients treated with standard of care".

Comparative Toxicity:

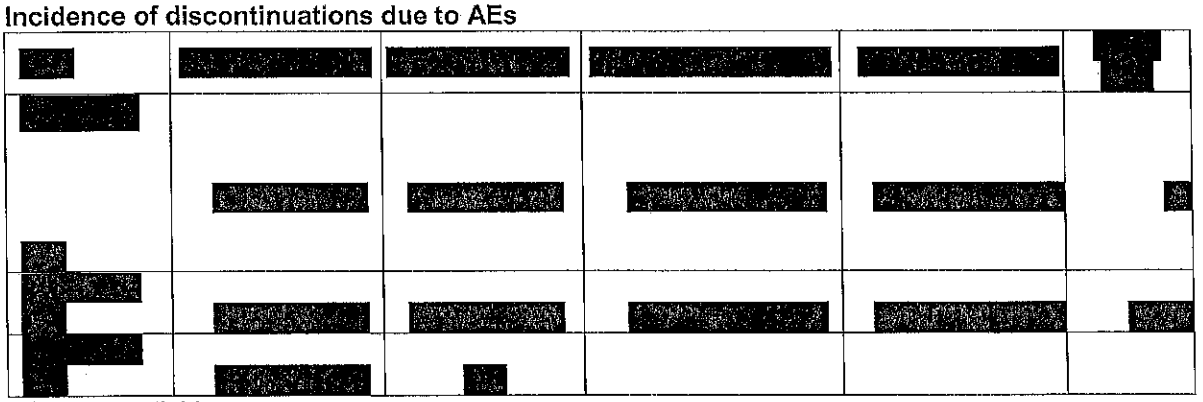
7.1.7 No new toxicity data were presented in the re-submission. Key toxicity data from the previous submission are reproduced in the following table:

Mean change from baseline in patient weight, total cholesterol and HDL cholesterol



N/A=not available; NR=not reported

Incidence of discontinuations due to AEs



N/A=not available

7.1.8 The sponsor agreed with the PBAC's comment that aripiprazole has a different safety profile to olanzapine, but stated that "the significant advantages identified with respect to weight gain and metabolic and endocrine parameters clearly outweigh the small numerical differences in adverse events seen between the two treatment arms". The basis of the re-submission's conclusion was unclear and did not appear to be supported by the incidence of discontinuations due to adverse events in the key trial.

Therapeutic Relativity:

7.1.9 The re-submission described aripiprazole as being no worse than olanzapine in terms of effectiveness and toxicity, with a different clinical profile.

7.1.10 The PBAC accepted the cost-minimisation claim against olanzapine but noted that no evidence had been presented in the re-submission to indicate a clinical superiority of aripiprazole over olanzapine.

7.1.11 The ESC advised that the equi-effective doses of the two drugs are as follows - aripiprazole 23.1mg/day and olanzapine 16.3mg/day. This relativity was based on the key

trial, CN-138-002. The dose of olanzapine was higher than that used by patients in Australia, and the dose of aripiprazole was higher than that likely to be by patients in Australia.

7.1.12 The PBAC noted the ESC advice that there were no clinically meaningful differences between 15mg and 30mg doses of aripiprazole.

Economic Evaluation:

7.1.13 An updated preliminary economic evaluation was presented. A cost-minimisation analysis was presented, whereas a cost-effectiveness approach was used in the previous submission. The resources included were drug costs. An additional non-trial based evaluation was presented including costs associated with relapse.

7.1.14 The trial-based incremental savings /patient was estimated to be [redacted] compared with [redacted] in the previous submission. In the non-trial based evaluation, cost savings resulting from switching patients from olanzapine to aripiprazole ranged from [redacted], depending on the scenario used.

7.1.15 An updated modelled economic evaluation was not presented, as a cost minimisation approach was presented. This was appropriate.

Estimated PBS Usage and Financial Implications:

7.1.16 The likely number of patients/year was estimated to be up to [redacted] in Year 4, compared to [redacted] patients in the previous submission. The decrease was due to alterations in population growth and substitution for all atypicals, and inclusion of only those patients using atypicals.

7.1.17 The financial savings/year to the PBS was estimated to be up to [redacted] in Year 4 using Scenario A, in which there was substitution of aripiprazole for olanzapine only. Under the four different scenarios, the expected savings range from [redacted] to [redacted]. This was compared to savings of [redacted] to [redacted] in the previous submission. The differences in estimated savings compared to the previous submission were due to the decrease in dispensed price for aripiprazole ([redacted] lower) and the substitution of other atypicals instead of substitution for olanzapine only.

Recommendation and Reasons:

7.1.18 The PBAC recommended listing on a cost-minimisation basis against olanzapine as no evidence to indicate a clinical superiority of aripiprazole over olanzapine had been presented. The equi-effective doses are 23.1 mg per day of aripiprazole and 16.3 mg per day of olanzapine, but it was noted that this dose of aripiprazole is higher than that likely to be used by patients in Australia and that this dose of olanzapine is higher than that used by patients in Australia. The PBAC noted that there is no evidence that doses greater than 15 mg per day of aripiprazole are more effective than 15 mg.

Recommendation:

List

ARIPIPRAZOLE 10mg, 15mg, 20mg, 30mg, tablets

Authority required

Schizophrenia.

Maximum quantity: 30
Repeats: 5