NICE advice

Schizophrenia: aripiprazole prolonged-release suspension for injection

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in March 2014. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Aripiprazole prolonged-release suspension for injection is licensed for maintenance treatment of schizophrenia in adults whose condition has been stabilised with oral aripiprazole. It was launched in the UK in January 2014. In 2 double-blind, randomised controlled trials (RCTs; n=403 and n=662), once-monthly aripiprazole 400 mg prolonged-release injection was shown to be superior to placebo and non-inferior to oral aripiprazole 10–30 mg daily in preventing relapse in adults with stabilised schizophrenia. The tolerability profile of the injectable formulation was similar to that of oral aripiprazole; the only new adverse event was injection-site reactions.

Effectiveness • In a double-blind RCT (n=403), aripiprazole prolonged-release injection statistically significantly delayed time to impending relapse compared with placebo (p<0.0001). • In a double-blind RCT (n=662), aripiprazole prolonged-release injection was non-inferior to oral aripiprazole 10–30 mg daily for the proportion of participants experiencing impending relapse (7.12% and 7.76% respectively). • No RCTs have directly compared aripiprazole prolonged-release injection with other antipsychotics.	**Safety** • Overall adverse event profile of aripiprazole prolonged-release injection was similar to that of oral aripiprazole, apart from injection-site reactions. • Common adverse events in the RCTs included weight gain (9%), akathisia (7.9%), insomnia (5.8%) and injection-site pain (5.1%).
User factors • Frequency of intramuscular injection is once every month into the gluteal muscle, compared with every 2 weeks for some other prolonged-release antipsychotic injections. • Side effect profile of aripiprazole may differ from that of other atypical antipsychotics. The BNF chapter on antipsychotic drugs describes the relative efficacy and adverse effects of different antipsychotics. A National Prescribing Centre patient decision aid provides a guide to the relative adverse effects of different antipsychotics, based on information available at that time (2009).	**Resource implications** • Annual drug acquisition cost of aripiprazole 400 mg prolonged-release injection is £2,645. • Annual drug acquisition cost of alternative depot antipsychotics (first and second-generation) ranges from £13 to £5,789, depending on the drug and dose. See the costs of selected treatment alternatives section for more information.

Key points

Schizophrenia is a major psychiatric disorder, or cluster of disorders, characterised by psychotic symptoms that alter a person's perception, thoughts, affect and behaviour.

In November 2013, aripiprazole prolonged-release suspension for injection (Abilify Maintena; a new, once-monthly formulation of aripiprazole) was granted a European marketing authorisation. It

is licensed for maintenance treatment of schizophrenia in adults whose condition has been stabilised with oral aripiprazole. It was launched in the UK in January 2014.

The recommended starting and maintenance dose is 400 mg, administered once a month into the gluteal muscle as a single intramuscular injection. After the first injection, treatment with oral aripiprazole (10–20 mg/day) should be continued for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy. If adverse events occur, reduction of the monthly dose to 300 mg should be considered. For people who have never taken aripiprazole, tolerability to oral aripiprazole should be established before starting treatment with aripiprazole prolonged-release injection.

This evidence review is based on 2 double-blind RCTs involving people with schizophrenia (Kane et al. 2012, Study 31-07-247 reported in the European public assessment report [EPAR] for Abilify Maintena). In the first study (Kane et al. 2012), 403 people whose condition had been stabilised on aripiprazole (oral for 4 to 12 weeks followed by prolonged-release injection for 12 to 36 weeks) were randomised to receive aripiprazole prolonged-release injection (400 mg with an option to decrease to 300 mg according to tolerability) or placebo injection once every 4 weeks for up to 52 weeks. Time to impending relapse in the double-blind phase (primary end point) was statistically significantly longer in people treated with aripiprazole prolonged-release injection than in those treated with placebo ($p<0.0001$). Treatment with aripiprazole prolonged-release injection was associated with statistically significantly lower impending relapse rates compared with placebo (10% compared with 39.6%).

In the second study (Study 31-07-247, reported in the EPAR for Abilify Maintena), 662 people whose condition had been stabilised on oral aripiprazole for at least 8 consecutive weeks were randomised to receive treatment with aripiprazole 400 mg prolonged-release injection once monthly (stepping down to 300 mg depending on tolerability), oral aripiprazole 10–30 mg daily, or aripiprazole 50 mg injection once monthly (stepping down to 25 mg depending on tolerability) . The aripiprazole prolonged-release 50 mg or 25 mg dose is an unlicensed dose and was included as a 'pseudo placebo' to test assay sensitivity for the non-inferiority design. Aripiprazole 400 mg or 300 mg prolonged-release injection was found to be non-inferior to oral aripiprazole for the primary outcome of the proportion of participants meeting impending relapse criteria at week 26 (7.12% and 7.76% respectively, estimated treatment difference −0.64%, 95% confidence interval [CI] −5.26 to 3.99). The secondary end points of time to impending relapse, proportion of people whose schizophrenia responded (defined as 'stabilised patients' at week 38), and proportion of people achieving remission did not differ significantly between the aripiprazole 400 mg or 300 mg prolonged-release injection and the oral aripiprazole groups. Aripiprazole 400 mg or 300 mg

injection was associated with a longer time to all-cause medication discontinuation than oral aripiprazole (figures not reported, $p<0.05$).

The adverse events profile of aripiprazole prolonged-release injection was similar to that of oral aripiprazole. The most frequently reported adverse events were weight gain, akathisia, insomnia and injection-site pain. Injection-site reactions were generally mild to moderate in severity and resolved over time. Extrapyramidal symptoms were reported more frequently with aripiprazole 400 mg or 300 mg prolonged-release injection than oral aripiprazole (18.4% compared with 11.7% patients, p value not reported).

Psychosis and schizophrenia in adults: treatment and management (NICE clinical guideline 178) recommends that depot or long-acting antipsychotics may be offered to people who would prefer such treatment after an acute episode of schizophrenia, or where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. NICE recommends that treatment with antipsychotic medication should be considered an explicit individual therapeutic trial (see Psychosis and schizophrenia in adults for more information).

The Medicines and Healthcare Products Regulatory Agency has warned that there is an increased risk of stroke and a small increased risk of death when antipsychotics are used in older people with dementia. The summary of product characteristics for Abilify Maintena states that it is not indicated for the treatment of people with dementia-related psychosis.

The place in therapy for this treatment is likely to be as an alternative treatment option to the currently available second-generation prolonged-release depot antipsychotics for maintenance treatment of schizophrenia. Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual factors for people with schizophrenia, when making decisions about using aripiprazole prolonged-release injection.

Key evidence

Kane JM, Sanchez M, Perry PP et al. (2012) Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. The Journal of Clinical Psychiatry 73: 617–24

European Medicines Agency (2013) European public assessment report: Abilify Maintena (EMEA/H/C/002755/0000) [online; accessed 15 January 2014]

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Relevance to NICE guidance programmes

Aripiprazole prolonged-release injection was not considered appropriate for a NICE technology appraisal, and is not currently planned into any other work programme.

In February 2014, NICE published Psychosis and schizophrenia in adults: treatment and management (NICE clinical guideline 178). NICE has also published a technology appraisal for oral aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years (NICE technology appraisal guidance 213).

Introduction

The NICE clinical guideline on psychosis and schizophrenia in adults describes schizophrenia as a major psychiatric disorder, or cluster of disorders, characterised by psychotic symptoms that alter a person's perception, thoughts, mood and behaviour. Each person with the disorder will have a unique combination of symptoms and experiences. NICE states that, over a lifetime, about 1% of the population will develop schizophrenia.

The NICE clinical guideline on psychosis and schizophrenia in adults recommends that people with a first episode of schizophrenia, or an acute exacerbation or recurrence of schizophrenia, should be offered oral antipsychotic medication in conjunction with psychological interventions. The NICE clinical guideline also recommends that depot or long-acting antipsychotics may be offered to people who would prefer such treatment after an acute episode of schizophrenia, or where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. When initiating depot or long-acting antipsychotics, the service user's preferences and attitudes towards regular intramuscular injections and organisational procedures (for example, home visits or location of clinics) should be taken into account.

The NICE clinical guideline recommends that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences). The BNF chapter on antipsychotic drugs describes the relative efficacy and adverse effects of different antipsychotics. A National Prescribing Centre patient decision aid provides a guide to the relative adverse effects of different antipsychotics, based on information available at that time (2009).

Product overview

Drug action

Aripiprazole is a second-generation antipsychotic. Similar to other second-generation antipsychotics, its exact mechanism of action is unknown. The Abilify Maintena summary of product characteristics states that aripiprazole's efficacy in schizophrenia may be mediated through a combination of partial agonist activity at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors.

New therapeutic indication

In November 2013, aripiprazole prolonged-release suspension for injection (Abilify Maintena; a new, once-monthly formulation of aripiprazole) was granted a European marketing authorisation. It is licensed for maintenance treatment of schizophrenia in adults whose condition has been stabilised with oral aripiprazole. It was launched in the UK in January 2014.

Course and cost

The once-monthly formulation of aripiprazole is provided as powder and solvent for prolonged-release suspension for injection. Each single-use vial contains aripiprazole 400 mg. It is intended for intramuscular injection into the gluteal muscle and should only be administered by a healthcare professional.

The recommended starting and maintenance dose is 400 mg once monthly (no sooner than 26 days after the previous injection) as a single injection. Titration of the dose is not needed. After the first injection, treatment with oral aripiprazole (10–20 mg) should be continued for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy. If adverse events

occur, reduction of the monthly dose to 300 mg should be considered (a 300 mg dose would be given from a 400 mg vial, if needed). In addition, dosage adjustments may be needed in people who are known to be CYP2D6 poor metabolisers, and people who are taking certain concomitant medications (see the Abilify Maintena summary of product characteristics for more information).

The summary of product characteristics states that for people who have never taken aripiprazole, tolerability to oral aripiprazole should be established before starting treatment with aripiprazole prolonged-release suspension for injection.

The cost of 1 vial of Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection for monthly use is £220.41 (MIMS March 2014).

Evidence review

This evidence summary is based on 2 randomised controlled trials (RCTs). The first study compared aripiprazole 400 mg once-monthly injections with placebo (Kane et al. 2012) and the second study (Study 31-07-247) compared aripiprazole once-monthly injections with oral aripiprazole 10–30 mg daily. The second study has not yet been fully published but the results are reported in detail in the European public assessment report (EPAR) for Abilify Maintena. The placebo-controlled study was terminated early for ethical reasons by an Independent Data Monitoring Committee on the basis of the results of a pre-planned interim analysis after 64 relapse events (final efficacy analysis included 80 relapse events) (Kane et al. 2012). The Independent Data Monitoring Committee determined that the primary end point had been achieved with no safety issues. Key efficacy and safety outcomes for the 2 studies are presented in tables 1 and 2.

Study 1: Kane et al. (2012)

- Design: 52-week double-blind, placebo-controlled RCT in 108 centres.
- Population: people aged 18 to 60 years (mean age 40.6 years) with a current diagnosis of schizophrenia (defined by Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision [DSM-IV-TR] criteria), a history of the disease for at least 3 years, and needing antipsychotic treatment. Participants had a history of relapse or symptom exacerbation when not receiving antipsychotic treatment. People were excluded if their history indicated that their schizophrenia was refractory to antipsychotic treatment, or if their condition had previously responded only to treatment with clozapine. Other exclusion criteria included a DSM-IV-TR diagnosis other than schizophrenia, any clinically significant medical or neurological disorder, and any medically significant abnormal laboratory test or electrocardiogram results at screening.

- Intervention and comparison: the study had a screening phase followed by 4 treatment phases. During the first treatment phase (4 to 6 weeks), participants receiving an antipsychotic drug other than aripiprazole were switched to oral aripiprazole monotherapy. During the second phase (4 to 12 weeks), all participants received oral aripiprazole (10–30 mg daily) until pre-specified stability criteria were achieved for 4 consecutive weeks. During the third phase, participants who met the criteria for stabilisation on oral aripiprazole received single-blind aripiprazole 400 mg prolonged-release injection every 4 weeks for up to 36 weeks. Participants also received oral aripiprazole 10–20 mg daily for the first 2 weeks of this phase to maintain therapeutic levels of antipsychotic medication during the transition from oral to prolonged–release injectable aripiprazole. The dose of prolonged-release aripiprazole could be reduced to 300 mg if adverse events were experienced. Participants (n=403) who met stability criteria for 12 consecutive weeks on prolonged-release aripiprazole entered the study's fourth phase and were randomised in a 2:1 ratio to double-blind treatment with aripiprazole prolonged-release injection (stabilisation dose, 96.3% received 400 mg) or placebo injection once every 4 weeks for up to 52 weeks. Antidepressants, mood stabilisers and antipsychotics other than aripiprazole were not permitted during the study.

- Outcomes: the primary outcome was time to exacerbation of psychotic symptoms or impending relapse from randomisation during the double-blind placebo-controlled phase. The key secondary outcome was the proportion of participants meeting impending relapse criteria during the double-blind phase. Other secondary outcomes included mean change from double-blind baseline to end point in Positive and Negative Syndrome Scale (PANSS) total score and mean change from baseline in Clinical Global Impression-Severity (CGI-S, range 1 [healthy, not ill] to 7 [among the most severely ill]) score. More information on rating scales and their clinical usefulness is available in review article by Mortimer (2007).

Exacerbation or impending relapse was defined as meeting 1 or more of the following criteria:

- Clinical worsening as defined by Clinical Global Impression-Improvement (CGI-I, range 1 [very much improved] to 7 [very much worse]) of 5 or more **and either**:
    - an increase on any of the following individual PANSS items (conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content) to a score of more than 4 with an absolute increase of 2 or more on that specific item since randomisation **or**
    - an increase on any of these PANSS items to a score of more than 4 and an absolute increase of 4 or more on the combined 4 PANSS items since randomisation.
- Hospitalisation due to worsening of psychotic symptoms.

- Clinical Global Impression-Severity of Suicide (CGI-SS) score of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 or a score of 6 (much worse) or 7 (very much worse) on Part 2.
- Violent behaviour resulting in clinically significant self-injury, injury to another person, or property damage.

Study 2: Study 31-07-247 **(as reported in the** EPAR for Abilify Maintena**)**

- Design: 38-week, multicentre, double-blind, non-inferiority RCT.
- Population: people aged 18 to 60 years (mean age 41.2 years) with a current diagnosis of schizophrenia (defined by DSM-IV-TR criteria), and a history of the illness for at least 3 years, and who were currently treated with an antipsychotic(s) other than clozapine. Participants had a history of relapse or symptom exacerbation when not receiving antipsychotic treatment. Exclusion criteria included people with a current DSM-IV-TR diagnosis other than schizophrenia.
- Intervention and comparison: the study had a screening phase followed by 3 treatment phases. During the first treatment phase (4 to 6 weeks), participants receiving an antipsychotic drug other than aripiprazole were converted to oral aripiprazole monotherapy. During the second phase, all enrolled participants had their schizophrenia stabilised with oral aripiprazole (10–30 mg daily) for a minimum of 8 consecutive weeks. During the third phase, 662 people who had met the criteria for stabilisation on oral aripiprazole were randomised in a 2:2:1 ratio to double-blind treatment with aripiprazole prolonged-release injection once monthly (400 mg with an option to decrease to 300 mg according to tolerability), oral aripiprazole 10–30 mg daily (stabilisation dose), or aripiprazole 50 mg (stepping down to 25 mg depending on tolerability) prolonged-release injection once monthly. The aripiprazole 50 mg or 25 mg prolonged-release dose was included as a 'pseudo placebo' to test assay sensitivity for the non-inferiority design. Allocation was concealed. Antidepressants, mood stabilisers and antipsychotics other than aripiprazole were not permitted during the study.
- Outcomes: the primary outcome was the estimated proportion of participants experiencing impending relapse (defined above) by end of 26 weeks from the date of randomisation in the double-blind phase. The primary efficacy analysis included all randomised participants (intention-to-treat [ITT] population). Secondary outcomes included time to impending relapse from randomisation during the double-blind phase, percentage of people whose schizophrenia responded (defined as 'stabilised patients' at week 38), percentage achieving remission (defined as score of 3 or less on specific PANSS items, maintained for 6 months), mean changes from baseline to end point in PANSS total score, PANSS positive and negative subscales,

personal and social performance (PSP) score, CGI-S, CGI-I score, and time to discontinuation due to all causes.

Table 1 Summary of study 1 (Kane et al. 2012)

	Aripiprazole PRI 400/ 300 mg once monthly[a]	Placebo	Analysis
Randomised	n=269	n=134	
Efficacy[b]	n=269	n=134	
Primary outcome: time to exacerbation of psychotic symptoms or impending relapse from randomisation[c]	Figures reported as Kaplan–Meier curves	Figures reported as Kaplan–Meier curves	Time to relapse was statistically significantly delayed in the aripiprazole PRI group compared with the placebo group (p≤0.0001)
Selected secondary outcomes:			
Proportion of participants with impending relapse during double-blind phase	10.0% (27/ 269)	39.6% (53/ 134)	Relapse rate statistically significantly lower with aripiprazole PRI compared with placebo (HR for placebo compared with aripiprazole 5.03, 95% CI 3.15 to 8.02)
Change from randomisation in mean PANSS total score[d]	+1.4	+11.6	Mean score increased (worsened) more with placebo compared with aripiprazole PRI (p<0.0001)
Change from randomisation in mean CGI-S score[d]	+0.1	+0.7	Mean score increased (worsened) more with placebo compared with aripiprazole PRI (p<0.0001)
Safety	n=269	n=134	
% participants with serious treatment-emergent adverse events during double-blind phase	4.1% (11/269)	6.7% (9/134)	p value not reported

% participants with adverse events leading to discontinuation during double-blind phase	7.1% (19/269)	13.4% (18/134)	p value not reported

Abbreviations: CI, confidence interval; CGI-S, clinical global impressions severity scale; HR, hazard ratio; n, number of participants; PANSS, positive and negative syndrome scale; PRI, prolonged release injection.

[a] Dose adjusted according to tolerability, 96.3% of participants received 400 mg.

[b] Primary efficacy analysis included all randomised participants.

[c] p value was derived from log-rank test for time to impending relapse.

[d] Increase in score indicates worsening.

Table 2 Summary of study 2 (Study 31-07-247 – as reported in the EPAR for Abilify Maintena)

	Aripiprazole PRI 400/300 mg once monthly[a]	Oral aripiprazole 10–30 mg daily	Aripiprazole PRI 50/25 mg once monthly[a]	Analysis
Randomised	n=265	n=266	n=131	
Efficacy[b]	n=265	n=266	n=131	
Primary outcome: estimated proportion of participants with impending relapse by week 26[c]	7.12% (SE 1.62)	7.76% (SE 1.72)	21.8% (SE 3.97)	Aripiprazole PRI 400/300 mg non-inferior[d] to oral aripiprazole (estimated treatment difference −0.64%, 95% CI −5.26 to 3.99) Aripiprazole PRI 400/300 mg superior to aripiprazole PRI 50/25 mg (difference −14.68, 95% CI −23.09 to −6.27, p=0.0006)
Selected secondary outcomes:				

Mean change in PANSS total score, baseline to week 38 (SE)	−1.66 (0.718)	+0.58 (0.714)	+3.08 (1.017)	Treatment differences: Aripiprazole PRI 400/300 mg compared with oral aripiprazole: −2.24; p=0.0272 Aripiprazole PRI 400/300 mg compared with. aripiprazole PRI 50/25 mg: −4.74; p=0.0002
Mean change in CGI-S, baseline to week 38 (SE)	−0.13 (0.049)	+0.05 (0.049)	+0.23 (0.070)	Treatment differences: Aripiprazole PRI 400/300 mg compared with oral aripiprazole: −0.17; p=0.0123 Aripiprazole PRI 400/300 mg compared with aripiprazole PRI 50/25 mg: −0.36; p<0.0001
Percentage of 'responders'[e]	89.8% (237/264)	89.4% (235/263)	75.2% (97/129)	No significant difference between aripiprazole PRI 400/300 mg and oral aripiprazole Proportion of 'responders' was statistically significant higher with aripiprazole PRI 400/300 mg compared with 50/25 mg (p=0.0001)
Proportion of participants achieving remission[f]	48.8% (105/215)	53.2% (107/201)	59.7% (43/72)	Difference between groups not significant

Abbreviations: CI, confidence interval; CGI-S, clinical global impressions-severity scale; n, number of participants; PANSS, positive and negative syndrome scale; PRI, prolonged-release injection; SE, standard error.

[a] Dose adjusted according to tolerability.

[b] Primary efficacy analyses were performed in the intention-to-treat population. No further detail on the intention-to-treat population provided in the EPAR.

[c] Relapse rates were estimated from the Kaplan–Meier curves for time to impending relapse at week 26.

[d] The 95% CI (−5.26 to 3.99) for the difference in the estimated proportion of participants experiencing impending relapse by the end of week 26 excluded the predefined non-inferiority margin of 11.5%.

[e] 'Responders' were defined as 'stabilised patients' at week 38.

[f] Remission defined as a score of 3 or less on each of the following specific PANSS items, maintained for a period of 6 months: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganisation (P2), mannerisms or posturing (G5), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6).

Clinical effectiveness

In the 2 studies described above, aripiprazole 400 mg or 300 mg prolonged-release injection was found to be non-inferior to oral aripiprazole 10–30 mg daily and more effective than placebo.

Kane et al. (2012) found that time to impending relapse in the double-blind phase (primary end point) was statistically significantly delayed in people treated with aripiprazole 400 mg or 300 mg prolonged-release injection compared with those treated with placebo ($p<0.0001$). At the final analysis point, treatment with aripiprazole 400 mg or 300 mg prolonged-release injection was also associated with statistically significantly lower impending relapse rates compared with placebo (10% compared with 39.6%, hazard ratio [HR] = 5.03, 95% confidence interval [CI] 3.15 to 8.02). Reasons for relapse for aripiprazole and placebo were clinical worsening according to CGI or PANSS (74.1% compared with 86.8% respectively); hospitalisation (25.9% compared with 9.4% respectively); suicide risk (3.7% compared with 1.9% respectively) and violent behaviour (3.7% compared with 7.5% respectively).

Time to study discontinuation (for all reasons other than study termination) was statistically significantly delayed with prolonged-release aripiprazole compared with placebo ($p\leq0.0001$) with discontinuation rates of 24.9% and 54.5% respectively.

In the active comparator study (study 31-07-247), aripiprazole 400 mg or 300 mg prolonged-release injection was found to be non-inferior to oral aripiprazole 10–30 mg daily for the primary outcome of proportion of participants meeting impending relapse criteria at week 26 (estimated relapse rates 7.12% and 7.76% respectively; between group difference −0.64%, 95% CI −5.26 to 3.99). The proportion of participants meeting impending relapse criteria at week 26 was statistically significant lower in the aripiprazole 400 mg or 300 mg group than in the low-dose aripiprazole 50 mg or 25 mg prolonged-release injection group (7.12% compared with 21.8%, p=0.0006).

The secondary end points of time to impending relapse, proportion of people whose schizophrenia responded, change in PSP total scores, and proportion achieving remission did not differ between the aripiprazole 400 mg or 300 mg prolonged-release and oral aripiprazole groups.

At week 38, CGI-S scores statistically significantly (p=0.0123) improved with aripiprazole 400 mg or 300 mg prolonged-release injection compared with oral aripiprazole. The mean CGI-I score at week 38 was better in the aripiprazole 400 mg or 300 mg prolonged-release injection group compared with the oral aripiprazole group (3.27 compared with 3.66 respectively, p=0.0002). The mean PANSS total score decreased (improved) from baseline in the aripiprazole 400 mg or 300 mg injection group but increased slightly in the oral aripiprazole group (−1.66 compared with +0.58, p=0.0272).

Sixty-seven (25.3%) people in the aripiprazole 400 mg or 300 mg prolonged-release injection group and 87 (32.7%) in the oral aripiprazole group discontinued study medication due to all causes by day 280. Aripiprazole 400 mg or 300 mg prolonged-release injection was associated with a longer time to discontinuation than oral aripiprazole (p=0.0484).

Preliminary results have been published (Kane et al. 2013) from a multicentre, open-label mirror-image study of 183 people (18–65 years) with schizophrenia, comparing total psychiatric hospitalisation rates between retrospective treatment with oral antipsychotics and prospective treatment with aripiprazole once monthly. After switching to aripiprazole once monthly, total psychiatric hospitalisation rates for the 3-month prospective period were statistically significantly lower (p<0.0001), compared with the retrospective 3-month period when the same participants received oral antipsychotics. The conclusions that can be drawn from this, however, are limited because this was a mirror-image study with no parallel active control and was open-label. As the authors acknowledge, it is difficult to separate treatment effect from trial effects and because the study was not blinded it is unknown what influence the study design had on the decision to hospitalise or not hospitalise.

Safety

The adverse event profile of aripiprazole prolonged-release injection appears similar to that of oral aripiprazole. The EPAR for Abilify Maintena states that the only new safety issue, compared with oral aripiprazole, is injection pain. Pooling data from both RCTs, the EPAR states that the rate of discontinuation during double-blind maintenance treatment as a result of an adverse event was 7.5% (40/534) in people who were treated with aripiprazole 400 mg or 300 mg prolonged-release injection, 7.1% (19/266) in those treated with oral aripiprazole and 13.4% (18/134) in those treated with placebo.

Serious treatment-emergent adverse events during double-blind treatment occurred in 4.9% (26/534) and 5.6% (15/266) of people who were treated with aripiprazole 400 mg/300 mg injection and oral aripiprazole respectively. The only serious adverse events reported by more than 1% of those receiving aripiprazole 400 mg or 300 mg injection were psychotic disorder and schizophrenia.

The most frequently reported adverse drug reactions in the trials in people who were treated with aripiprazole 400 mg or 300 mg prolonged-release injection were weight gain (9.0%), akathisia (7.9%), insomnia (5.8%) and injection-site pain (5.1%). Injection-site reactions were generally mild to moderate in severity and resolved over time. Extrapyramidal symptoms were reported more frequently with aripiprazole 400 mg or 300 mg injection than oral aripiprazole (98/534 [18.4%] people compared with 31/266 [11.7%] people, p value not reported). The most frequently observed extrapyramidal symptoms were akathisia events followed by parkinsonism events (EPAR for aripiprazole prolonged-release injection).

The EPAR states that in the active comparator study (Study 31-07-247), a higher incidence of potentially clinically relevant low white blood cell count (leukopenia) was observed in the aripiprazole 400 mg or 300 mg prolonged-release injection group compared with the oral aripiprazole group (2.3% compared with 0.8%). Pooling data from both RCTs, the EPAR states that during the double-blind maintenance phases, treatment-emergent adverse events relating to white blood cell abnormalities occurred in 0.6% (3/534) people who were treated with aripiprazole 400 mg or 300 mg prolonged-release injection, 0.4% (1/266) in those treated with oral aripiprazole 10–30 mg daily and 0.8% (1/131) in those treated with aripiprazole 50 mg or 25 mg prolonged-release injection. The abnormality in each group was neutropenia.

The Medicines and Healthcare Products Regulatory Agency has warned that there is an increased risk of stroke and a small increased risk of death when antipsychotics are used in older people with dementia. The summary of product characteristics for Abilify Maintena states that it is not indicated for the treatment of dementia-related psychosis.

Evidence strengths and limitations

The 2 RCTs reviewed were adequately designed and were considered by the Committee for Medicinal Products for Human Use to be of sufficient duration (longer than 6 months in the double-blind phase) to support the indication of maintenance treatment in schizophrenia. In the active comparator study (Study 31-07-247) allocation was concealed, therefore avoiding an important potential source of bias.

However, the studies have some limitations. Before randomisation, people had their schizophrenia stabilised on aripiprazole for at least 16 weeks in the first study (4 weeks oral, 12 weeks injection, Kane et al. 2012) and 8 weeks in the second (oral, Study 31-07-247). This may have resulted in selection bias towards people who tolerated, and whose schizophrenia responded to, aripiprazole. The Committee for Medicinal Products for Human Use considered that although people who were included in study 31-07-247 were sufficiently representative of the intended population, relapse rates were lower than anticipated and the long duration of stabilisation may have been a factor contributing to this.

The studies report whether or not treatments had a statistically significant effect on several rating scales used to assess treatment response in schizophrenia. However, whether statistically significant effects on these scales are also clinically significant is difficult to establish.

The active comparator study (study 31-07-247) was a non-inferiority design. European Medicines Agency guidance on the points to consider on switching between superiority and non-inferiority advises that, although in a superiority study the intention-to-treat analysis is the analysis of choice, in a non-inferiority study the intention-to-treat and per-protocol analyses have equal value and their use should lead to similar conclusions for a robust interpretation of the results. The EPAR states that primary efficacy analyses were performed for all participants belonging to the intention-to-treat dataset, and that other analyses excluding participants who were unblinded, and duplicate-entry participants, revealed comparable results. However, it is not clear from the limited detail in the EPAR if this represents per-protocol analyses, and therefore it isn't clear if the robustness of the results was supported.

Long-term safety data for the prolonged-release formulation of aripiprazole are currently limited. An ongoing open-label safety study (NCT01129882) should provide more data. In addition, the EPAR for Abilify Maintena indicates that a post-authorisation safety study has been requested to further investigate extrapyramidal symptoms.

From these studies, it is not known how aripiprazole prolonged-release injection compares with other long-acting antipsychotic injections or oral antipsychotics. A 28-week, randomised open-label study (QUALIFY) comparing the effectiveness of aripiprazole 400 mg or 300 mg once monthly with paliperidone palmitate 50–150 mg once monthly in people with schizophrenia is currently ongoing (NCT01795547).

Context

Treatment alternatives

The NICE clinical guideline on psychosis and schizophrenia recommends that people with a first episode of schizophrenia, or an acute exacerbation or recurrence of schizophrenia, should be offered oral antipsychotic medication in conjunction with psychological interventions. The NICE clinical guideline also recommends that depot or long-acting antipsychotics may be offered to people who would prefer such treatment after an acute episode of schizophrenia, or where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.

The NICE clinical guideline recommends that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences). The BNF chapter on antipsychotic drugs describes the relative efficacy and adverse effects of different antipsychotics. A National Prescribing Centre patient decision aid provides a guide to the relative adverse effects of different antipsychotics, based on information available at that time (2009).

Costs of selected treatment alternatives

All drugs in the table below are prolonged-release intramuscular injections. The table includes both first (haloperidol, fluphenazine, flupentixol, pipotiazine, and zuclopenthixol) and second (aripiprazole, risperidone, olanzapine, and paliperidone) generation antipsychotics.

	Dose regimen[a]	Cost per year excluding VAT[b]
Aripiprazole	400 mg once monthly	£2,645

Risperidone	25–50 mg every 2 weeks	£2,072 to £3,712
Olanzapine pamoate	150–300 mg every 2 weeks or 300–405 mg every 4 weeks	£2,894 to £5,789
Paliperidone palmitate	25–150 mg once monthly	£2,207 to £4,711
Haloperidol decanoate	50–300 mg every 4 weeks	£50 to £197
Fluphenazine decanoate	12.5–100 mg every 2 to 5 weeks	£13 to £227
Flupentixol decanoate	50 mg every 4 weeks to 300 mg every 2 weeks	£49 to £156
Pipotiazine palmitate	50–100 mg every 4 weeks	£212 to £347
Zuclopenthixol decanoate	200–500 mg every 1 to 4 weeks	£26 to £189
[a] Doses taken from the relevant summary of product characteristics. The doses shown may not represent the full range that can be used and they do not imply therapeutic equivalence. [b] Costs taken from MIMS, February 2014.		

Estimated impact for the NHS

Likely place in therapy

It is likely that aripiprazole prolonged-release injection will be used as an alternative treatment option to the currently available second-generation prolonged-release depot antipsychotics for maintenance treatment for schizophrenia in adults.

The NICE clinical guideline on psychosis and schizophrenia in adults recommends that treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. It also recommends that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences). The BNF chapter on

antipsychotic drugs describes the relative efficacy and adverse effects of different antipsychotics. A National Prescribing Centre patient decision aid provides a guide to the relative adverse effects of different antipsychotics, based on information available at that time (2009).

The dosing schedule of aripiprazole prolonged-release injection has potential advantages over some currently available depot antipsychotics because it is given monthly rather than fortnightly and initial dose titration is not needed.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual factors for people with schizophrenia, when making decisions about using aripiprazole prolonged-release injection. The publication of head-to-head studies comparing the efficacy and adverse event profile of aripiprazole prolonged-release injection with other antipsychotics, including the less costly first-generation antipsychotic depot injections, would facilitate a better understanding of its place in the treatment of schizophrenia.

Estimated usage

The manufacturer estimates that 15,245 people in England are currently receiving a second-generation prolonged-release antipsychotic for maintenance treatment for schizophrenia. They predict that 4% of those eligible for treatment with these drugs will receive aripiprazole prolonged-release in year 1 rising to 8% in year 2 and 12% in year 3 (Otsuka Pharmaceutical Limited: personal communication, January 2014).

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About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines integrated process statement.

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