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Aripiprazole

In the Treatment of Irritability Associated with Autistic Disorder in Pediatric Patients

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Contents

Abstract

Aripiprazole is an atypical antipsychotic approved for the treatment of irritability associated with autistic disorder in pediatric patients aged 6–17 years.

In two, randomized, double-blind, placebo-controlled studies in pediatric patients aged 6–17 years with irritability associated with autistic disorder, 8 weeks of treatment with aripiprazole 2–15 mg/day, compared with placebo, resulted in significant improvements in the Aberrant Behavior Checklist Irritability subscale score at endpoint (primary endpoint), and the mean Clinical Global Impression-Improvement score.

Aripiprazole was generally well tolerated in this patient population in the two 8-week studies and a 52-week study, with most adverse events being mild to moderate in severity. Aripiprazole was associated with weight gain in both the short- and long-term studies; data from the long-term study indicated that the increase in bodyweight reached a plateau at 3–6 months.

Features and properties of aripiprazole (Abilify®)	
Featured indication	
Treatment of irritability associated with autistic disorder in pediatric patients aged 6–17 y	
Mechanism of action	
Partial dopamine D_2 and serotonin 5-HT_{1A} receptor agonist; serotonin 5-HT_{2A} receptor antagonist	
Dosage and administration in the featured indication	
Recommended dose	5–10 mg
Initial dose	2 mg
Maximum dose	15 mg
Frequency	Once daily
Route of administration	Oral
Pharmacokinetic profile in a study in children and adolescents receiving 2–15 mg/d for 14 d[1]	
Mean peak plasma concentration (C_{max})	43.8–194.2 ng/mL
Median time to C_{max}	2–4 h
Mean area under the plasma concentration-time curve	800–3879 ng • h/mL
Mean apparent steady-state clearance	0.03–0.07 L/h/kg
Adverse events (incidence ≥5% and at least twice that with placebo in clinical trials in pediatric patients aged 6–17 y with irritability associated with autistic disorder)[2]	
Sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy	

Autistic disorder is a neurodevelopmental disorder with childhood onset.[3] It is characterized by atypical development in social interaction, communication, and play, and the presence of restricted and repetitive behaviors.[3] Moderate or severe behavioural problems, such as irritability, are commonly experienced by patients with autistic disorder, and further impair social intervention and communication, placing a considerable burden on individuals and their families.[3,4]

While there are no approved treatments for the core symptoms of autistic disorder, various pharmacologic options have been investigated for treating the associated behavioural symptoms.[5] Currently, the atypical antipsychotics risperidone[6] and aripiprazole (Abilify®)[7] are approved by the US FDA for use in the treatment of irritability (including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods) associated with autistic disorder in pediatric patients.

This profile focuses on the pharmacological characteristics, therapeutic efficacy, and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric patients aged 6–17 years. Although aripiprazole has been approved by the FDA for various indications in children and adolescents (including the treatment of schizophrenia in patients aged 13–17 years,[8] and the acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in patients aged 10–17 years[7,9]), a discussion of its use in these indications is beyond the scope of this review.

Medical literature (including published and unpublished data) on the use of aripiprazole in the treatment of irritability associated with autistic disorder was identified by searching databases since 1996 (including MEDLINE, EMBASE and in-house AdisBase), bibliographies from published literature, clinical trial registries/databases, and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug. Searches were last updated 5 February 2011.

1. Pharmacodynamic Profile

- The therapeutic efficacy (see section 3) of aripiprazole, a quinolinone derivative, is thought primarily to be mediated through the partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors, and its antagonism at the 5-HT_{2A} receptor.[7,10,11]
- Partial agonistic activity is also shown at D_3 and D_4 receptors and 5-HT_{2C} and 5-HT_7 receptors.[7,10,11] Aripiprazole acts as an antagonist at the 5-HT_{2B} and 5-HT_6 receptors.

Table I. Affinity of atypical aripiprazole for G-protein-coupled receptors[7,11]

Receptor	K_i (nmol/L)
Dopamine	
D_2	0.34
D_3	0.8
D_4	44
Serotonin	
5-HT_{1A}	1.7
5-HT_{2A}	3.4
5-HT_{2C}	15
5-HT_7	39
Other	
α_1-Adrenergic	57
Histamine H_1	61
Serotonin reuptake site	98

K_i = mean inhibitory constant.

- Aripiprazole binds with high affinity to D_2 and D_3, 5-HT_{1A} and 5-HT_{2A} receptors, with moderate affinity to D_4, 5-HT_{2C}, and 5-HT_7, α_1-adrenergic, H_1 receptors, and the serotonin reuptake site (see table I).[7,10] Aripiprazole exhibits minimal affinity for muscarinic or cholinergic receptors (50% inhibition occurring at >1000 nmol/L).
- The major metabolite of aripiprazole dehydro-aripiprazole also binds to dopamine D_2 receptors and displays pharmacological activity similar to that of the parent compound.[10,11]
- A dose-dependent increase in dopamine D_2 receptor occupancy was observed in brain tissue of healthy male volunteers receiving aripiprazole 0.5–30 mg/day (assessed using positron emission tomography).[12] Across this dosage range, occupancy ranged from approximately 40–95%.

2. Pharmacokinetic Profile

Data from this section have largely been obtained from a study in children and adolescents aged 6–17 years with conduct disorders administered once-daily aripiprazole for 14 days.[1] Twenty patients received aripiprazole 2–15 mg/day. Data have also been obtained from the manufacturer's prescribing information.[7]

- At steady state, the pharmacokinetic profile of aripiprazole was linear (across the dosage range 2–15 mg/day) in children and adolescents[1] and, after correction for differences in bodyweight, was consistent with those reported in adults.[7,10] Steady-state plasma concentrations of aripiprazole were reached within 14 days.[1]

• In children and adolescents receiving aripiprazole 2–15 mg/day, mean steady-state peak plasma concentrations (C_{max}) were 43.8–194.2 ng/mL, and were reached in a median 2–4 hours.[1] Mean area under the plasma concentration-time (AUC) curve values were 800–3879 ng • h/mL.[1]

• Absolute bioavailability of aripiprazole after oral administration is 87%.[7] The drug is 99% protein bound, and is distributed to intravascular and extravascular compartments (including the brain).[7,10,12]

• Aripiprazole is metabolized by cytochrome P450 (CYP) 3A4 and 2D6 enzymes by dehydrogenation, hydroxylation, and N-dealkylation pathways.[7] The major metabolite is dehydro-aripiprazole (representing 15–32% of the AUC of the parent drug at steady state in the study in children and adolescents[1]).

• In adults, the apparent terminal elimination half-life ($t_{½\beta}$) of aripiprazole was approximately 75 hours in extensive metabolizers of CYP2D6 and 146 hours in poor metabolizers.[7] The mean $t_{½\beta}$ of dehydro-aripiprazole was approximately 94 hours.

• The mean apparent steady-state clearance of aripiprazole 2–15 mg/day was 2.53 L/h in children and 3.85 L/h in adolescents; the difference between the two age groups was eliminated when normalized for weight (0.03–0.07 L/h/kg)[1] and was consistent with that previously reported in adults.[13]

• Approximately 25% (<1% unchanged) and 55% (≈18% unchanged) of a single radiolabelled oral dose of aripiprazole administered to adults was eliminated in the urine and faeces, respectively.[7]

• Sex, race, hepatic status, and renal status had no clinically relevant effect on the pharmacokinetic profile of aripiprazole.[7]

• Aripiprazole is a substrate of CYP2D6 and CYP34A enzymes, and consequently may be subject to drug interactions with strong inducers or inhibitors of these enzymes.[11] In adults, coadministration of aripiprazole with CYP3A4 inducers (e.g. carbamazepine[14]) reduces aripiprazole exposure; increases of the aripiprazole dosage are recommended when coadministration with these agents occurs.[7] Conversely, coadministration of aripiprazole with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole) or CYP2D6 inhibitors (e.g. quinidine) increases aripiprazole exposure; reductions in the aripiprazole dosage are advised when coadministration of these agents occurs.[7]

• The pharmacokinetics of drugs metabolized by CYP enzymes are not expected to be affected by coadministration with aripiprazole.[7] Aripiprazole had no clinically significant effect on the pharmacokinetics of omeprazole (a CYPC219 substrate), warfarin (a CYP2C9 and CYP2C19 substrate), or dextromethorphan (a CYP2D6 and CYP3A4 substrate). In addition, no clinically important drug interactions were reported in adults when aripiprazole was coadministered with therapeutic dosages of escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine, valproate, famotidine, lorazepam, lithium, or lamotrigine.[7]

Table II. Trial design, baseline patient (pt) characteristics and inclusion/exclusion criteria for two 8-wk, randomized, double-blind, placebo-controlled, multicenter, phase III trials that investigated the efficacy of aripiprazole (ARI) for the treatment of irritability associated with autistic disorder[15,16]

Parameter	Flexible-dosage trial Owen et al.[15] (n = 98)	Fixed-dosage trial Marcus et al.[16] (n = 218)
Mean pt age (y)	9.3	9.7
Pts aged 6–12 y (%)	85	76
Male pts (%)	88	89
Mean pt weight (kg)	42.2	42.9
Pts administered ≥1 concomitant CNS medication (%)	36	33
Inclusion criteria	Age 6–17 y Met DSM-IV-TR diagnostic criteria for autistic disorder[3] Diagnosis confirmed by ADI-R[17] An ABC-I[18] subscale score ≥18 and a CGI-S score ≥4 at screening and baseline Demonstrated serious behavioral problems (e.g. tantrums, aggression, self-injurious behavior, or a combination of these problems)	
Exclusion criteria	Current diagnosis of bipolar disorder, psychosis, schizophrenia or major depression, fragile X syndrome, or diagnosis of another disorder on the autism spectrum, including pervasive developmental disorders, Asperger's disorder, Rett disorder, or childhood disintegrative disorder History of neuroleptic malignant syndrome; a significant risk for committing suicide; seizure in the past year; history of severe head trauma or stroke; history or current evidence of any unstable medical conditions; or a laboratory test, vital sign, or electrocardiogram result considered clinically significant Treatment resistant to antipsychotic medication or had a known allergy or hypersensitivity to aripiprazole	

ABC-I = Aberrant Behavior Checklist-Irritability subscale; **ADI-R** = Autism Diagnostic Interview-Revised; **CGI-S** = Clinical Global Impression-Severity; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision.

Table III. Efficacy assessment measures used in aripiprazole trials in children and adolescents with irritability associated with autistic disorder (see table IV)[15,16,19]

Assessment measure	Acronym	Description
Aberrant Behavior Checklist Irritability subscale score	ABC-I	A caregiver-rated 15-item subscale (score of 0–45) that measures the emotional and behavioural symptoms of irritability in autistic disorder, including deliberate self-injuriousness, aggressiveness to other children and adults, temper tantrums, and quickly changing moods; a decrease from baseline in score indicates improvement
Clinical Global Impression-Severity score	CGI-S	A clinician-rated scale where 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = extremely ill
Clinical Global Impression-Improvement score	CGI-I	A clinician-rated scale where 1 = very much improved at endpoint; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse
Responders		No. of patients with a ≥25% reduction in the ABC-I subscale score and CGI-I score ≤2

3. Therapeutic Efficacy

Short-Term Trials

Trial Design

The efficacy of oral aripiprazole in the treatment of irritability associated with autistic disorder has been investigated in two randomized, double-blind, placebo-controlled, multicenter trials in pediatric patients aged 6–17 years.[15,16] Patients demonstrated behaviors such as tantrums, self-injurious behavior, aggression, or a combination of these behaviors. The baseline characteristics of the patients, and the inclusion and exclusion criteria for these two trials are summarized in table II. Details of efficacy assessment measures used in the trials are given in table III.

Both trials involved a screening period of up to 42 days, followed by an 8-week treatment phase in which patients were randomized to aripiprazole.[15,16] In one trial (flexible-dosage trial), patients were randomized (1 : 1) to aripiprazole (2–15 mg/day; with target dosages of 5, 10 or 15 mg/day[15]) or placebo. In the other trial (fixed-dosage trial), patients were randomized (1 : 1 : 1 : 1) to a fixed dosage of aripiprazole (5, 10 or 15 mg/day) or placebo.[16]

Trial Outcomes

- Aripiprazole was efficacious in reducing irritability associated with autistic disorder in pediatric patients.[15,16] Mean improvements from baseline at week 8 in the caregiver-rated Aberrant Behavior Checklist Irritability (ABC-I) subscale score (primary endpoint) was significantly greater with aripiprazole than placebo, according to data from each of the 8-week trials ($p < 0.05$; see table IV).[15,16]
- A *post hoc* analysis of data from both trials suggests that improvements in irritability were primarily due to improvements in behavior related to tantrums.[20] Across both trials, and in the flexible dosage trial alone, significantly greater improvements with aripiprazole than with placebo occurred for the following individual items of the ABC-I subscale: 'rapid mood changes', 'cries/screams inappropriately', and 'stamps feet/bangs objects' ($p < 0.05$).[20]
- In addition, significantly greater improvements with aripiprazole than with placebo occurred with the following items of the ABC-I scale in the flexible dosage trial[15] and in at least one arm of the fixed-dose trial:[16] 'aggressive towards others', 'screams inappropriately', 'temper tantrums', 'irritable', 'yells', 'demands must be met immediately', 'cries over minor hurts', and 'temper outbursts' ($p < 0.05$).[20]
- Aripiprazole compared with placebo was associated with significantly greater improvements in irritability symptoms as measured by the mean clinician-rated Clinical Global Impression-Improvement score at week 8 (secondary endpoint) in both trials ($p < 0.01$; see table IV).[15,16]
- The change from baseline in the clinician-rated Clinical Global Impression-Severity (CGI-S) score at week 8 (secondary endpoint) was significantly greater with aripiprazole than placebo in the flexible dosage trial ($p < 0.001$; see table IV).[15] The between-group difference in the change from baseline in the CGI-S score for aripiprazole 10 or 15 mg/day versus placebo was significant in the fixed-dose trial ($p < 0.05$).[16]
- Aripiprazole appeared to improve health-related quality of life.[15,16] The Pediatric Quality of Life Inventory combined scales total score significantly improved with aripiprazole 2–15 mg/day versus placebo in the flexible-dose trial (least-squares

mean treatment different [TD] 11.4; 95% CI 6.1, 16.8)[15] and with aripiprazole 15 mg/day only versus placebo in the fixed-dose trial (TD 8.2; 95% CI 1.2, 15.2).[16]

- Aripiprazole also appeared to reduce caregiver burden.[15,16] The Caregiver Strain Questionnaire global score demonstrated improvements with aripiprazole 2–15 mg/day versus placebo in the flexible-dose trial (TD −1.9; 95% CI −2.7, −1.2),[15] and with aripiprazole 15 mg/day versus placebo in the fixed-dose trial (TD −1.1; 95% CI −1.9, −0.3).[16]
- A significantly greater proportion of aripiprazole than placebo recipients responded to treatment (see table IV) in the flexible-dose trial ($p < 0.001$).[15] In the fixed-dose trial,[16] the response rate was significantly greater with aripiprazole than with placebo only with the lower dosage of 5 mg/day ($p < 0.05$).

Long-Term Treatment

An open-label, multicenter trial investigated the efficacy of flexibly dosed aripiprazole 2–15 mg/day in pediatric patients aged 6–17 years in the treatment of irritability associated with autistic disorder (data obtained from the manufacturer's clinical trial database[19]).

Table IV. Efficacy of once-daily oral aripiprazole (ARI) in pediatric patients (pts) aged 6–17 years with irritability associated with autistic disorder[a]

Study	Treatment (mg/day)	No. of pts[b]	ABC-I[c]		CGI-S[c]		CGI-I[c,d]	Responders[c,d] (% of pts)
			baseline	change from baseline[d]	baseline	change from baseline[d]		
8-wk, randomized, double-blind, placebo (PL)-controlled, multicenter trials[e]								
Flexible dosage								
Owen et al.[15]	ARI 2–15	46	29.6	−12.9***[f]	4.9	−1.2***	2.2***	52.2***
	PL	49	30.8	−5.0[f]	4.8	−0.4	3.6	14.3
Fixed dosage								
Marcus et al.[16]	ARI 5	52	28.6	−12.4*[f]	5.0	−0.9	2.6**	55.8*
	ARI 10	59	28.2	−13.2**[f]	4.9	−1.0*[g]	2.5***	49.2
	ARI 15	53	28.9	−14.4***[f]	5.1	−1.1*[g]	2.5***	52.8
	PL	49	28.0	−8.4[f]	4.7	−0.6	3.3	34.7
52-wk, open-label, multicenter trial								
Manufacturer's clinical trial database[19]	ARI 2–15 (*de novo* pts[h])	80	23.2	−6.5	4.8	−0.8		
	ARI 2–15 (PL rollover[h])	68	21.5	−6.1	4.2	−0.4		
	ARI 2–15 (ARI rollover)[h]	166	15.0	+0.7	3.9	0		

a See table III for definitions of ABC-I, CGI-I, and CGI-S.

b The efficacy population included all pts who had received at least one dose of the study drug and who had at least one efficacy evaluation during the treatment phase, with the last observation carried forward. Data were evaluated using an analysis of covariance adjusted for treatment, baseline weight category (≥40 kg or <40 kg), study centre, and baseline value.

c See table III for description.

d At wk 8[15,16] or wk 52.[19]

e In both 8-wk trials, ARI was initiated at a dose of 2 mg/d and then titrated up to 5 mg/d during the second wk. In the flexible-dose trial, ARI then increased in 5 mg increments up to 15 mg/d based on clinical response; no dose increase occurred in the last 2 wk of the trial. At any time, the ARI dosage could be adjusted downwards for tolerability at the discretion of the investigator.[15] In the fixed-dose trial,[16] ARI was then increased in increments of 5 mg/wk to the assigned dose.

f Primary endpoint.

g p-Value for treatment difference = difference in adjusted treatment mean changes; ARI vs PL.

h *De novo* pts had not participated in either of the previous 8-wk trials; rollover pts had received either PL or ARI in the 8-wk trials.[15,16]

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PL.

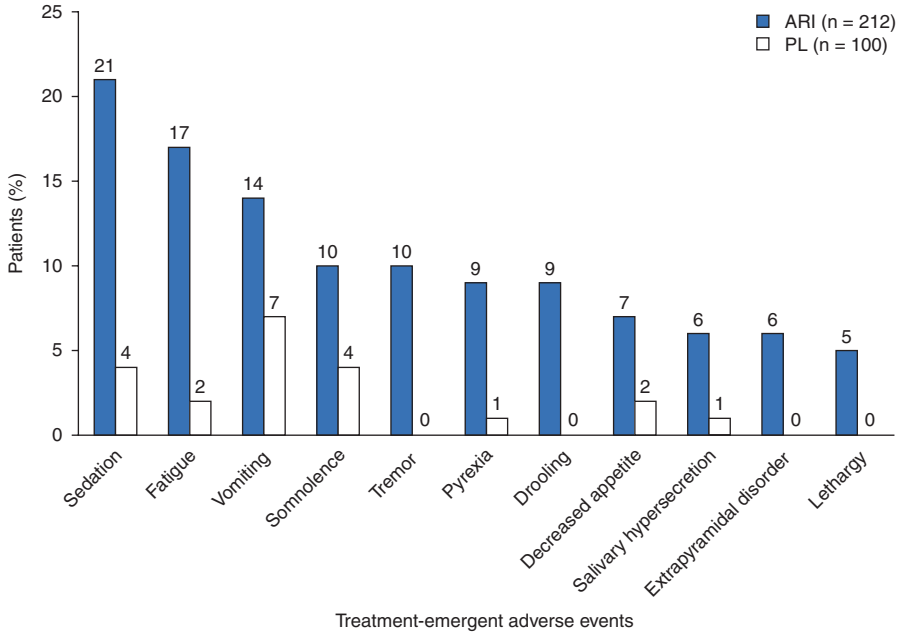

Fig. 1. Tolerability of oral aripiprazole (ARI) in pediatric patients aged 6–17 years with irritability associated with autistic disorder. Treatment-emergent adverse events that occurred with an incidence ≥5% in ARI recipients and at least 2-fold higher in ARI than in placebo (PL) recipients who received at least one dose of the study medication are reported.[2] Combined data were obtained from a *post hoc* analysis of two 8-week, randomized, double-blind, multicenter trials in which pediatric patients received ARI (administered as a flexible dose of 2–15 mg/day[15] or a fixed dose of 5, 10, or 15 mg/day) or PL.[16]

Patients who completed either of the two 8-week trials,[15,16] and who continued to meet all inclusion criteria and none of the exclusion criteria, were eligible for entry into a 52-week, open-label trial.[19] Patients who did not participate in either of these trials (*de novo*) were also eligible to enter the trial provided that they met the same inclusion criteria as those of the 8-week trials (see table II).

- Aripiprazole appeared to maintain efficacy in the long term.[19] Although the evaluation of efficacy in the 52-week trial was only a secondary endpoint, the mean change from baseline at week 52 in measures of efficacy (including ABC-I and CGI-S scores) indicated that the improvements seen after 8 weeks of treatment in the two randomized, double-blind trials[15,16] were maintained when the patients continued with aripiprazole treatment over the longer duration (see table IV).

4. Tolerability

Short-Term Trials

- Short-term aripiprazole treatment was generally well tolerated in pediatric patients with irritability associated with autistic disorder, with most adverse events being mild or moderate in severity, according to data from each of the 8-week trials,[15,16] and a *post hoc* analyses of combined data from the two 8-week trials (313 patients who received at least one dose of the study medication).[2]
- Fatigue appeared to be associated with a dose-related response (see figure 1 for the incidence of this adverse event in the fixed-dose trial[16]).
- Common adverse events associated with short-term aripiprazole treatment (occurring with an incidence of ≥5% in aripiprazole recipients and at least 2-fold higher in aripiprazole than in placebo recipients) in the two 8-week trials included sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy (see figure 1).[2]
- The peak incidence of onset for these treatment-emergent adverse events was week 1 or 2, with the exception of tremor (week 3), nasopharyngitis (week 3), extrapyramidal disorder (week 4), drooling (week 5), diarrhea (week 2 and 5), and cough (week 7).[2] Generally, most adverse events resolved over time in aripiprazole recipients; the median time to resolution of the sedation, fatigue, vomiting, and somnolence was 19, 26, 1, and 23 days, respectively.
- The overall rate of discontinuation due to an adverse event was 10% with aripiprazole and 7% with placebo in the 313 patients who received at least one dose of the study medication in the 8-week trials.[2]
- Non-akathisia extrapyramidal symptom-related events were reported in 18% of aripiprazole versus 2% of placebo recipients; the respective incidence of akathisia-related events was 3% versus 9%.[2] There was a significant difference between

aripiprazole and placebo treatment in the change from baseline to endpoint in the Simpson Angus Scale[21] (+0.1 vs −0.4; $p = 0.03$), but not the Barnes Akathisia Rating Scale.[22]

- Aripiprazole, compared with placebo, was associated with weight gain in the two 8-week trials (1.6 vs 0.4 kg; $p \leq 0.001$).[2,7] Clinically significant weight gain (≥7% relative to baseline) was reported in 26% of aripiprazole recipients and 7% of placebo recipients.[7]
- Aripiprazole 2–15 mg/day had minimal effects on mean fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or triglyceride levels.[2]
- Aripiprazole, compared with placebo, was associated with significant decreases at endpoint in serum prolactin levels (all $p < 0.001$).[15,16] Potentially clinically relevant changes in prolactin levels at endpoint were reported in none of the aripiprazole recipients and 4.4% of the placebo recipients in the fixed-dose trial;[16] respective incidences were 2.4% and 6.8% in the flexible-dose trial.[15]
- Aripiprazole was not associated with any clinically relevant changes in vital signs or any clinically relevant electrocardiogram abnormalities.[15,16]

Long-Term Trial

- In pediatric patients with irritability associated with autistic disorder, the tolerability profile of aripiprazole over the long term was consistent with that over the short term.[15,16] Long-term treatment with flexible-dose aripiprazole 2–15 mg/day was well tolerated, according to data from the 52-week, open-label trial (presented in an abstract[23] and the manufacturer's clinical trial database[19]).
- The most common treatment-emergent adverse events (≥10% of patients) with long-term aripiprazole treatment were weight gain (23%), vomiting (19%), nasopharygnitis (13%), increased appetite (13%), pyrexia (12%), upper respiratory tract infection (12%), and insomnia (10%). EPS-related events were reported in 15% of patients, with tremor being most commonly reported (3%).[19,23]
- Most adverse events appeared early after treatment initiation and generally resolved.[19] Based on body mass index and weight z-scores, the increase in bodyweight reached a plateau at 3–6 months.[19]
- The incidence of aripiprazole recipients who had baseline levels of metabolic parameters within normal limits and who subsequently had treatment-emergent abnormalities at any point in the trial was generally low.[23] The incidence of treatment-emergent abnormalities in total cholesterol, LDL-C, triglycerides, glucose, or glycosylated haemoglobin levels was ≤7%, with the exception of abnormalities in HDL-C (21%).

5. Dosage and Administration

The recommended dosage of aripiprazole for the treatment of irritability associated with autistic disorder in pediatric patients aged 6–17 years is 5–10 mg/day.[7]

The recommended starting dosage of aripiprazole 2 mg/day should be increased to 5 mg/day, with subsequent increases to 10 or 15 mg/day depending on the tolerability of the drug and the response of the individual. Dosage adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week.

The US label for aripiprazole carries a black-box warning regarding an increased risk for suicidality in children, adolescents, and young adults with major depressive disorders and other psychiatric disorders.[7] Aripiprazole is not approved for use in pediatric patients with depression. The US label for aripiprazole also carries a black-box warning for increased mortality in elderly patients with dementia-related psychosis.

Detailed information regarding the use of aripiprazole in other indications and special patient populations, contraindications, warnings, precautions, and drug interactions can be obtained from the manufacturer's prescribing information.[7]

6. Aripiprazole: Current Status in the Treatment of Irritability Associated with Autistic Disorder in Pediatric Patients

Oral aripiprazole is approved by the FDA for use in the treatment of irritability associated with autistic disorder in pediatric patients (aged 6–17 years).[7] In two, well designed, 8-week trials in this patient population, aripiprazole was more effective than placebo in improving scores on the ABC-I subscale. Aripiprazole was generally well tolerated after short- or long-term treatment, with most adverse events being mild to moderate in severity and resolving with continued treatment. Although aripiprazole was associated with weight gain in both short- and long-term trials, the increase in bodyweight reached a plateau at 3–6 months, and no clinically relevant changes in metabolic parameters were reported.

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