EU の添付文書及びその和訳
ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

ABILIFY 5 mg tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 5 mg of aripiprazole.
For excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Tablet
The tablets are rectangular and blue, engraved with A-007 and 5 on one side.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

ABILIFY is indicated for the treatment of schizophrenia.

4.2 **Posology and method of administration**

Oral use.

The recommended starting and maintenance dose for ABILIFY is 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 15 to 30 mg/day. Enhanced efficacy at doses higher than the recommended daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

**Children and adolescents:** ABILIFY has not been studied in subjects under 18 years of age.

**Patients with hepatic impairment:** no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

**Patients with renal impairment:** no dosage adjustment is required in patients with renal impairment.

**Elderly:** the effectiveness of ABILIFY in the treatment of schizophrenia in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

**Gender:** no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

**Smoking status:** according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).
When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

4.3 Contraindications

ABILIFY is contraindicated in patients with hypersensitivity to aripiprazole or to any of the excipients.

4.4 Special warnings and special precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored throughout this period.

Tardive Dyskinesia: in premarketing studies of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In premarketing studies, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including ABILIFY, must be discontinued.

Seizure: in premarketing studies, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Cerebrovascular Adverse Events, including stroke, in elderly patients with dementia-related psychosis: in three placebo-controlled trials of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse events (e.g. stroke, transient ischemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse events compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. ABILIFY is not approved for the treatment of dementia-related psychosis.

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4.5 Interaction with other medicinal products and other forms of interaction

Due to its \( \alpha_1 \)-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken in combination with alcohol or other CNS drugs with overlapping side effects such as sedation (see section 4.8).

Potential for other medicinal products to affect ABILIFY:

A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

In a clinical study in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while \( C_{\text{max}} \) was unchanged. The AUC and \( C_{\text{max}} \) of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

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Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of \( C_{\text{max}} \) and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of \( C_{\text{max}} \) and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

When either valproate or lithium were administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations.

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), 2C9 (warfarin), 2C19
(omeprazole), and 3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism \textit{in vitro}. Thus, aripiprazole is unlikely to cause clinically important drug interactions mediated by these enzymes.

4.6 **Pregnancy and lactation**

**Pregnancy:**
There are no adequate and well-controlled studies of aripiprazole in pregnant women. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

**Lactation:**
Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 **Effects on ability to drive and use machines**

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely.

4.8 **Undesirable effects**

The following undesirable effects occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse drug reactions (*):

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Common} ($&gt; 1/100, &lt; 1/10$): lightheadedness, insomnia, akathisia, somnolence, tremor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Common} ($&gt; 1/100, &lt; 1/10$): blurred vision</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Uncommon} ($&gt; 1/1,000, &lt; 1/100$): tachycardia*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Uncommon} ($&gt; 1/1,000, &lt; 1/100$): orthostatic hypotension*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Common} ($&gt; 1/100, &lt; 1/10$): nausea, vomiting, dyspepsia, constipation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Common} ($&gt; 1/100, &lt; 1/10$): headache, asthenia</td>
</tr>
</tbody>
</table>

Extrapyramidal symptoms (EPS): in a long term 52-week controlled study, aripiprazole-treated patients had an overall-lower incidence (27.1%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (59.2%). In a long term 26-week placebo-controlled study, the incidence of EPS was 20.3% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled study, the incidence of EPS was 16.8% for aripiprazole-treated patients and 15.7% for olanzapine-treated patients.

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory parameters revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.9% of aripiprazole treated patients as compared to 3.6% of patients who received placebo.
Other findings:
Undesirable effects known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse events in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Post-Marketing

The following adverse events have also been reported very rarely during post-marketing surveillance (the calculation for the frequency is based on an estimate of patient exposure):

Immune system disorders: allergic reaction (e.g. anaphylactic reaction, angioedema, pruritus, or urticaria)
Psychiatric disorders: nervousness, agitation
Nervous system disorders: speech disorder
Vascular disorders: syncope
Gastrointestinal disorders: increased salivation, pancreatitis
Musculoskeletal, connective tissue and bone disorders: stiffness, myalgia, rhabdomyolysis
General disorders and administration site conditions: chest pain
Investigations: increased Creatine Phosphokinase, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST)

4.9 Overdose

In clinical studies, accidental or intentional acute overdosage of aripiprazole was identified in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhea, and somnolence.

During post-marketing experience, the reported signs and symptoms observed in adult patients who overdosed with aripiprazole alone at doses up to 450 mg included tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole (up to 195 mg) in children have been received. The potentially medically serious signs and symptoms reported included extrapyramidal symptoms and transient loss of consciousness.

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple drug involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C<sub>max</sub> by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics, ATC code; N05 AX12
It has been proposed that aripiprazole’s efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity in vitro for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole. Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Further information on clinical trials:
Schizophrenia: in three short-term (4 to 6 week) placebo-controlled trials involving 1,228 schizophrenic patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medication at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Weight gain: in clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N=18, or 13% of evaluable patients), compared to olanzapine (N=45, or 33% of evaluable patients).

5.2 Pharmacokinetic properties

Absorption:
Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:
Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-ariumiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Metabolism:
Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.
Elimination:
The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

Following a single oral dose of $[^{14}C]$-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Elderly:
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:
Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

Preclinical safety data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (3 to 14 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (14 times the mean steady-state AUC at the maximum recommended human dose).

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m$^2$). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of in vitro solubility.
Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Indigo carmine E132 aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

ABILIFY tablets are available in aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Commonwealth House, 2 Chalkhill Road
Hammersmith - London W6 8DW - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/001-005
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 June 2004

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg tablets

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Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of $C_{\text{max}}$ and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of $C_{\text{max}}$ and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

When either valproate or lithium were administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations.

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), 2C9 (warfarin), 2C19
(omeprazole), and 3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism in vitro. Thus, aripiprazole is unlikely to cause clinically important drug interactions mediated by these enzymes.

4.6 Pregnancy and lactation

Pregnancy:
There are no adequate and well-controlled studies of aripiprazole in pregnant women. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Lactation:
Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breastfeed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely.

4.8 Undesirable effects

The following undesirable effects occurred more often (≥ 1/100) than placebo, or were identified as possibly medically relevant adverse drug reactions (*):

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Extrapyramidal symptoms (EPS): in a long term 52-week controlled study, aripiprazole-treated patients had an overall-lower incidence (27.1%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (59.2%). In a long term 26-week placebo-controlled study, the incidence of EPS was 20.3% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled study, the incidence of EPS was 16.8% for aripiprazole-treated patients and 15.7% for olanzapine-treated patients.

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory parameters revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.9% of aripiprazole treated patients as compared to 3.6% of patients who received placebo.
Other findings:
Undesirable effects known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse events in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Post-Marketing

The following adverse events have also been reported very rarely during post-marketing surveillance (the calculation for the frequency is based on an estimate of patient exposure):

- **Immune system disorders:** allergic reaction (e.g. anaphylactic reaction, angioedema, pruritis, or urticaria)
- **Psychiatric disorders:** nervousness, agitation
- **Nervous system disorders:** speech disorder
- **Vascular disorders:** syncope
- **Gastrointestinal disorders:** increased salivation, pancreatitis
- **Musculoskeletal, connective tissue and bone disorders:** stiffness, myalgia, rhabdomyolysis
- **General disorders and administration site conditions:** chest pain
- **Investigations:** increased Creatine Phosphokinase, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST)

4.9 Overdose

In clinical studies, accidental or intentional acute overdosage of aripiprazole was identified in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhea, and somnolence.

During post-marketing experience, the reported signs and symptoms observed in adult patients who overdosed with aripiprazole alone at doses up to 450 mg included tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole (up to 195 mg) in children have been received. The potentially medically serious signs and symptoms reported included extrapyramidal symptoms and transient loss of consciousness.

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple drug involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C<sub>max</sub> by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics, ATC code; N05 AX12
It has been proposed that aripiprazole’s efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity in vitro for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole. Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Further information on clinical trials:
Schizophrenia: in three short-term (4 to 6 week) placebo-controlled trials involving 1,228 schizophrenic patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medication at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Weight gain: in clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N=18, or 13% of evaluable patients), compared to olanzapine (N=45, or 33% of evaluable patients).

5.2 Pharmacokinetic properties

Absorption:
Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:
Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-apripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Metabolism:
Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.
Elimination:
The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

Following a single oral dose of [14C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Elderly:
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:
Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

Preclinical safety data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (3 to 14 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (14 times the mean steady-state AUC at the maximum recommended human dose).

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m²). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of in vitro solubility.
Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Red iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

ABILIFY tablets are available in aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Commonwealth House, 2 Chalkhill Road
Hammersmith - London W6 8DW - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/006-010
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 June 2004

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

ABILIFY 15 mg tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 15 mg of aripiprazole. 
For excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Tablet
The tablets are round and yellow, engraved with A-009 and 15 on one side.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

ABILIFY is indicated for the treatment of schizophrenia.

4.2 **Posology and method of administration**

Oral use.

The recommended starting and maintenance dose for ABILIFY is 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 15 to 30 mg/day. Enhanced efficacy at doses higher than the recommended daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

**Children and adolescents:** ABILIFY has not been studied in subjects under 18 years of age.

**Patients with hepatic impairment:** no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

**Patients with renal impairment:** no dosage adjustment is required in patients with renal impairment.

**Elderly:** the effectiveness of ABILIFY in the treatment of schizophrenia in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

**Gender:** no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

**Smoking status:** according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).
When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

4.3 Contraindications

ABILIFY is contraindicated in patients with hypersensitivity to aripiprazole or to any of the excipients.

4.4 Special warnings and special precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored throughout this period.

Tardive Dyskinesia: in premarketing studies of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In premarketing studies, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including ABILIFY, must be discontinued.

Seizure: in premarketing studies, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Cerebrovascular Adverse Events, including stroke, in elderly patients with dementia-related psychosis: in three placebo-controlled trials of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse events (e.g. stroke, transient ischemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse events compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. ABILIFY is not approved for the treatment of dementia-related psychosis.

Hyperglycaemia and Diabetes Mellitus: hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse events (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.
4.5 Interaction with other medicinal products and other forms of interaction

Due to its α₁-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken in combination with alcohol or other CNS drugs with overlapping side effects such as sedation (see section 4.8).

Potential for other medicinal products to affect ABILIFY:

A gastric acid blocker, the H₂ antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

In a clinical study in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical study in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors, may be expected to have similar effects and similar dose reductions should therefore be applied.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

When either valproate or lithium were administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations.

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In clinical studies, 10-30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), 2C9 (warfarin), 2C19.
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4.6 Pregnancy and lactation

Pregnancy:
There are no adequate and well-controlled studies of aripiprazole in pregnant women. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Lactation:
Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

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As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely.

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Undesirable effects known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse events in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

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<tr>
<td>Gastrointestinal disorders</td>
<td>increased salivation, pancreatitis</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>stiffness, myalgia, rhabdomyolysis</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>chest pain</td>
</tr>
<tr>
<td>Investigations</td>
<td>increased Creatine Phosphokinase, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST)</td>
</tr>
</tbody>
</table>

4.9 Overdose  
In clinical studies, accidental or intentional acute overdosage of aripiprazole was identified in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhea, and somnolence.

During post-marketing experience, the reported signs and symptoms observed in adult patients who overdosed with aripiprazole alone at doses up to 450 mg included tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole (up to 195 mg) in children have been received. The potentially medically serious signs and symptoms reported included extrapyramidal symptoms and transient loss of consciousness.

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple drug involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole $C_{\text{max}}$ by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES  
5.1 Pharmacodynamic properties  
Pharmacotherapeutic group: antipsychotics, ATC code; N05 AX12
It has been proposed that aripiprazole’s efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity in vitro for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole. Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Further information on clinical trials:
Schizophrenia: in three short-term (4 to 6 week) placebo-controlled trials involving 1,228 schizophrenic patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo. ABILIFY is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medication at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over halperidol. In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Weight gain: in clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N=18, or 13% of evaluable patients), compared to olanzapine (N=45, or 33% of evaluable patients).

5.2 Pharmacokinetic properties

Absorption:
Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:
Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Metabolism:
Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.
Elimination:
The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

Following a single oral dose of $[^{14}C]$-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Elderly:
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:
Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

Preclinical safety data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (3 to 14 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (14 times the mean steady-state AUC at the maximum recommended human dose).

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m$^2$). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of in vitro solubility.
Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Yellow iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

ABILIFY tablets are available in aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Commonwealth House, 2 Chalkhill Road
Hammersmith - London W6 8DW - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/011-015
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 June 2004

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of aripiprazole.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
The tablets are round and pink, engraved with A-011 and 30 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia.

4.2 Posology and method of administration

Oral use.

The recommended starting and maintenance dose for ABILIFY is 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 15 to 30 mg/day. Enhanced efficacy at doses higher than the recommended daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Children and adolescents: ABILIFY has not been studied in subjects under 18 years of age.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).
When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

4.3 Contraindications

ABILIFY is contraindicated in patients with hypersensitivity to aripiprazole or to any of the excipients.

4.4 Special warnings and special precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored throughout this period.

Tardive Dyskinesia: in premarketing studies of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In premarketing studies, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including ABILIFY, must be discontinued.

Seizure: in premarketing studies, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Cerebrovascular Adverse Events, including stroke, in elderly patients with dementia-related psychosis: in three placebo-controlled trials of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse events (e.g. stroke, transient ischemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse events compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. ABILIFY is not approved for the treatment of dementia-related psychosis.

Hyperglycaemia and Diabetes Mellitus: hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse events (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.
4.5 Interaction with other medicinal products and other forms of interaction

Due to its $\alpha_1$-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken in combination with alcohol or other CNS drugs with overlapping side effects such as sedation (see section 4.8).

Potential for other medicinal products to affect ABILIFY:

A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

In a clinical study in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while $C_{\text{max}}$ was unchanged. The AUC and $C_{\text{max}}$ of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical study in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and $C_{\text{max}}$ by 63% and 37%, respectively. The AUC and $C_{\text{max}}$ of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors, may be expected to have similar effects and similar dose reductions should therefore be applied.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of $C_{\text{max}}$ and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of $C_{\text{max}}$ and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

When either valproate or lithium were administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations.

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), 2C9 (warfarin), 2C19.
(omeprazole), and 3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism in vitro. Thus, aripiprazole is unlikely to cause clinically important drug interactions mediated by these enzymes.

4.6 Pregnancy and lactation

Pregnancy:
There are no adequate and well-controlled studies of aripiprazole in pregnant women. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Lactation:
Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely.

4.8 Undesirable effects

The following undesirable effects occurred more often (≥ 1/100) than placebo, or were identified as possibly medically relevant adverse drug reactions (*):

| Nervous system disorders | Common (≥ 1/100, < 1/10): lightheadedness, insomnia, akathisia, somnolence, tremor |
| Eye disorders | Common (≥ 1/100, < 1/10): blurred vision |
| Cardiac disorders | Uncommon (≥ 1/1000, < 1/100): tachycardia* |
| Vascular disorders | Uncommon (≥ 1/1000, < 1/100): orthostatic hypotension* |
| Gastrointestinal disorders | Common (≥ 1/100, < 1/10): nausea, vomiting, dyspepsia, constipation |
| General disorders and administration site conditions | Common (≥ 1/100, < 1/10): headache, asthenia |

Extrapyramidal symptoms (EPS): in a long term 52-week controlled study, aripiprazole-treated patients had an overall-lower incidence (27.1%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (59.2%). In a long term 26-week placebo-controlled study, the incidence of EPS was 20.3% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled study, the incidence of EPS was 16.8% for aripiprazole-treated patients and 15.7% for olanzapine-treated patients.

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory parameters revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.9% of aripiprazole treated patients as compared to 3.6% of patients who received placebo.
Other findings:
Undesirable effects known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse events in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Post-Marketing

The following adverse events have also been reported very rarely during post-marketing surveillance (the calculation for the frequency is based on an estimate of patient exposure):

- Immune system disorders: allergic reaction (e.g. anaphylactic reaction, angioedema, pruritis, or urticaria)
- Psychiatric disorders: nervousness, agitation
- Nervous system disorders: speech disorder
- Vascular disorders: syncope
- Gastrointestinal disorders: increased salivation, pancreatitis
- Musculoskeletal, connective tissue and bone disorders: stiffness, myalgia, rhabdomyolysis
- General disorders and administration site conditions: chest pain
- Investigations: increased Creatine Phosphokinase, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST)

4.9 Overdose

In clinical studies, accidental or intentional acute overdosage of aripiprazole was identified in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhea, and somnolence.

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Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple drug involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C\text{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

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Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.
Elimination:
The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

Following a single oral dose of $[^{14}C]$-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Elderly:
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:
Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

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An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m²). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of in vitro solubility.
Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate
Red iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

ABILIFY tablets are available in aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Commonwealth House, 2 Chalkhill Road
Hammersmith - London W6 8DW - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/016-020
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 June 2004

10. DATE OF REVISION OF THE TEXT
ABILIFY™
SUMMARY OF PRODUCT CHARACTERISTICS
製品特性概要書

1. 製品名
ABILIFY 5mg 錠

2. 組成・成分
ABILIFY 5mg 錠は 1 錠中にアリピプラゾール 5mg を含有する。
添加物については、6.1 参照。

3. 性状
錠剤
錠剤は長方形で青色をしており、片面に A-007 及び 5 と刻印されている。

4. 臨床特性

4.1 効能・効果
ABILIFY は、統合失調症の治療に用いられる。

4.2 用法・用量
経口投与する。

ABILIFY の推奨開始用量及び維持用量は 15mg/日で、食事の摂取に関係なく 1 日 1 回服用する。

ABILIFY は、15～30mg/日の用量範囲で有効である。さらに高い用量で効果を得られる患者があるかもしれないが、推奨用量である 15mg/日を超える用量で有効性が増大することは示されていない。最大投与量は 30mg/日を超えないこと。

小児及び思春期の患者：18 歳未満の患者を対象にした試験は実施されていない。

肝障害患者：軽度から中等度の肝障害患者に対し用量調整の必要はない。重度の肝障害を有する患者に対しての推奨用量を示すには現在のところ十分なデータは得られていない。従って、慎重に投与管理を行うこと。また重度の肝障害患者における最大用量である 30mg/日の投与は慎重に行うこと（5.2 参照）。

腎障害患者：腎障害患者に対し用量調整の必要はない。
高齢者：65 歳以上の統合失調症患者における ABILIFY の治療効果は確立されていない。高齢者は感受性がより高いため、臨床的な要因から必要と考えられる場合は通常以下の投与開始量も考慮すること（4.4 参照）。

性別：男女間で用量調整の必要はない（5.2 参照）。

喫煙状況：ABILIFY の代謝経路から、喫煙者に対し用量調整の必要はない（4.5 参照）。

CYP3A4 或いは CYP2D6 の強力な阻害薬とアリビプラゾールを併用する場合、アリビプラゾールの用量を減量すること。CYP3A4 或いは CYP2D6 阻害薬を併用療法からはずす場合は、アリビプラゾールを増量すること（4.5 参照）。

CYP3A4 を強力に誘導する薬剤とアリビプラゾールを併用する場合、アリビプラゾールの用量を増量すること。CYP3A4 を誘導する薬剤を併用療法からはずす場合は、アリビプラゾールを推奨用量まで減量すること（4.5 参照）。

4.3 禁忌
本剤又は本剤の添加物に対し過敏症のある患者には、ABILIFY を投与しないこと。

4.4 警告及び使用上の注意
抗精神病薬による治療では、患者の臨床症状改善には数日から数週間かかる可能性がある。この間、患者を注意深く観察すること。

遲発性ジスキネジア：1 年以内の投与期間で実施された市販前の臨床試験において、アリビプラゾール投与下でのジスキネジアの発現がときに報告された。ABILIFY 服用中の患者に遅発性ジスキネジアの徴候や症状が発現した場合は、投与量の減量或いは投薬中止を考慮すること。これらの症状は、投与中止後に一時的に悪化したり或いは発現する場合もある。

悪性症候群（NMS）：悪性症候群（NMS）は抗精神病薬の投与に伴う、致死的な恐れのある症状の複合体である。市販前の臨床試験において、アリビプラゾール投与中 NMS の発現が稀に報告された。NMS の臨床症状としては、異常高熱、筋強直、精神状態の変化及び自律神経系の不安定さ（脈拍又は血圧の変動、頻脈、発汗及び不整脈）がある。さらに CPK の上昇、ミオグロビン尿症（横紋筋融解症）及び急性腎不全が発現することもある。患者が NMS を疑わせる徴候及び症状、或いは NMS の臨床症状を伴わないが原因不明の高熱を発現した場合、ABILIFY を含むすべての抗精神病薬の投与を中止すること。

痙攣：市販前の臨床試験において、アリビプラゾールを投与中に痙攣を発現した報告がときにある。このため、痙攣障害の既往或いは痙攣に関連する症状のある患者へのアリビプラゾールの使用については慎重に行うこと。
痴呆に関連する精神病症状を有する高齢患者における脳卒中を含む脳血管性の有害事象：アルツハイマー病に伴う精神病症状を有する高齢患者を対象としたアリビブラゾールの3種のプラセボ対照試験において、死亡例を含む脳血管性の有害事象（脳卒中、一過性脳虚血発作など）を発現した患者（平均年齢：84歳；範囲：78-88歳）が報告された。これらの試験の集計で、アリビブラゾール投与患者の1.3%に脳血管性の有害事象が報告されたのに対し、プラセボ投与患者では0.6%、この差は統計学的に有意ではなかった。しかしこれらの試験のうちの1つである固定用量試験では、痴呆に関連する精神病症状に対するアリビブラゾールを投与された患者において脳血管性の有害事象に関して有意な用量反応関係が認められた。なお ABILIFY は、痴呆に関連する精神病症状の治療に対しては承認されていない。

高血糖・糖尿病：非定型抗精神病薬を投与されている患者において高血糖の報告があり、一部では、ケトアシドーシス、高浸透圧性昏睡を伴う顕著な症例、あるいは死亡に至る症例も報告されている。アリビブラゾールの臨床試験において、糖尿病を含む高血糖関連の有害事象又は血糖値異常の発現頻度にプラセボとの有意差は認められなかった。ABILIFY 及び他の非定型抗精神病薬を投与された患者間で高血糖関連の有害事象を直接比較できるような正確なリスク評価は行われていない。ABILIFY を含む非定型抗精神病薬を投与されている患者については、多飲、多尿、脱力感などの高血糖の徴候・症状がないかを観察し、糖尿病又はその危険因子を有する患者については、血糖値のコントロールが悪化していないかを定期的にモニターすべきである。

4.5 他の医薬品との相互作用及びその他の相互作用
アリビブラゾールは、α1, α2アドレナリン受容体拮抗作用によりある種の降圧薬の作用を増強する可能性がある。

アリビブラゾールが主として中枢神経系に作用することを考慮して、ABILIFY とアルコール或いは鎮静等の副作用が重複する他の中枢作用薬と併用する場合は注意すること（4.8参照）。

ABILIFY 対する他剤の影響：
胃酸分泌抑制剤である H2拮抗剤ファモジンは、アリビブラゾールの吸収率を低下させるが、この作用に臨床的な意義はないと考えられる。

アリビブラゾールは、CYP2D6 及び CYP3A4 が関与する複数の経路により代謝されるが、CYP1A によっては代謝されない。従って、喫煙者に対し用量調整の必要はない。

健康人を対象とした臨床試験において、CYP2D6 の強力な阻害薬（キニジン）はアリビブラゾールのAUCを107%増加させたが、Cmaxに変化はなかった。活性代謝物塩化ビドロアリビブラゾールのAUCは32%，Cmaxは47%減少した。キニジンと併用する場合は、ABILIFY を処方された用量の約1/2に減量すること。フルオキセチン及びパロキセチン
等その他の CYP2D6 の強力な阻害薬については、同様の作用が予測されるため、同様の減量をすること。

健康人を対象とした臨床試験において、CYP3A4 の強力な阻害薬（ケトコナゾール）はアリビプラゾールの AUC 及び Cmax をそれぞれ 63% と 37% 増加させた。活性代謝物デヒドロアリビプラゾールの AUC は 77%, Cmax は 43% 増加した。CYP2D6 の代謝能の低い被験者 (poor metabolizer) で代謝能の高い被験者 (extensive metabolizer) に比べ、CYP3A4 の強力な阻害薬を ABILIFY と併用すると、アリビプラゾールの血漿中濃度が高くなる可能性がある。ケトコナゾール或いは他の強力な CYP3A4 阻害薬と ABILIFY の併用を考慮する場合には、患者に対する潜在的ベネフィットが潜在的リスクを上回らなければならない。ケトコナゾールを ABILIFY と併用する場合、ABILIFY を処方量の約半分に減量する。イトラコンゾール及び HIV プロテアーゼ阻害薬等、その他の CYP3A4 の強力な阻害薬は同様の作用が予測されるため、同様の減量をすること。

CYP2D6 或いは CYP3A4 阻害薬の併用投与を中止した時は、ABILIFY の用量を併用療法開始前のレベルまで増量すること。

CYP3A4 の強力な誘導薬であるカルバマゼピンを併用投与後、アリビプラゾールの Cmax 及び AUC の幾何平均値は、アリビプラゾール（30mg）単独投与時と比べて、それぞれ 68% 及び 73% 低かった。同様にカルバマゼピン投与後のデヒドロアリビプラゾールの Cmax 及び AUC の幾何平均値は、アリビプラゾール単独投与時に比べて、それぞれ 69% 及び 71% 低かった。

カルバマゼピンと ABILIFY を併用する場合、ABILIFY の用量を 2 倍に増量すること。その他の強力な CYP3A4 誘導薬（例、リファンピシン、リファブチン、フェニトイン、フェノバルビタール、ブリミドン、エファビレンツ、ネビラビン及びセント・ジョンズ・ワート）でも同様の作用が予測されるため、同様の増量をすること。CYP3A4 の強力な誘導薬の併用投与を中止した時は、ABILIFY を推奨用量まで減量すること。

バルプロア酸塩あるいはリチウムをアリビプラゾールと併用した場合、アリビプラゾールの血中濃度に臨床上意義のある変化はみられなかった。

他剤に対する ABILIFY の影響：

臨床試験において、アリビプラゾールの用量 10～30mg/日は、CYP2D6（デキストロメトールほど/β-メトキシメチルフィナノフ）CYP2C9（ワルファリン）、CYP2C19（オメプラゾール）及び CYP3A4（デキストロメトール）の基質の代謝に重大な影響を及ぼさなかった。また in vitro において、アリビプラゾールとデヒドロアリビプラゾールが CYP1A2 を介する代謝に影響を及ぼす可能性も認められなかった。従って、アリビプラゾールがこれらの酵素を介する臨床上重要な薬剤相互作用を起こす可能性は低い。
4.6 妊婦及び授乳婦

妊娠：
妊娠を対象とした適切で十分にコントロールされたアリビプラゾール投与試験は実施されていない。動物試験では、発生毒性の可能性を除外できなかった（5.3 参照）。アリビプラゾール投与期間中に妊娠した場合又は妊娠を希望する場合は、医師にその旨連絡するよう患者を指導すること。ヒトにおける安全性の情報が不十分であり、動物での生殖発生毒性試験に基づく懸念もあるため、本剤投与により期待される利益が胎児への潜在的リスクを明らかに上回る正当な理由がない限り、本剤を妊娠に投与しないこと。

授乳：
ラットの授乳期にアリビプラゾールを投与すると乳汁中に移行した。アリビプラゾールがヒトの乳汁中に移行するか否かは不明である。アリビプラゾール服用中は授乳を避けよう患者を指導すること。

4.7 運転及び機械操作能力に与える影響
他の抗精神薬と同様、アリビプラゾールによる影響がないことを合理的に確認できるまで、自動車の運転を含む危険な機械を操作する場合には患者に注意を促すこと。
### 4.8 副作用
ブラセボ群よりも発現頻度の高い有害事象（≥1/100），或いは医学的に意義があると考えられる副作用(*)を下記に示す。

<table>
<thead>
<tr>
<th>神経系障害</th>
<th>一般的な事象（&gt;1/100, &lt;1/10）：頭部ふらふら感，不眠症，アカシジア，傾眠，振戦</th>
</tr>
</thead>
<tbody>
<tr>
<td>眼障害</td>
<td>一般的な事象（&gt;1/100, &lt;1/10）：霧視</td>
</tr>
<tr>
<td>心臓障害</td>
<td>ときに起こる事象（&gt;1/1,000, &lt;1/100）：頻脈*</td>
</tr>
<tr>
<td>血管障害</td>
<td>ときに起こる事象（&gt;1/1,000, &lt;1/100）：起立性低血圧*</td>
</tr>
<tr>
<td>胃腸障害</td>
<td>一般的な事象（&gt;1/100, &lt;1/10）：嘔気，嘔吐，消化不良，便秘</td>
</tr>
<tr>
<td>全身障害および投与局所様態</td>
<td>一般的な事象（&gt;1/100, &lt;1/10）：頭痛，無力症</td>
</tr>
</tbody>
</table>

錐体外路系症状（EPS）：52 過間の長期ハロペリドール対照試験において，パーキンソン病，アカシジア，ジストニア，及びジスキネジアを含む EPS の発現率は，アリビプラゾール群（27.1%）がハロペリドール群（59.2%）に比べて全体的に低かった。26 過間の長期プラセボ対照試験における EPS の発現率は，アリビプラゾール群で 20.3％，ブラセボ群で 13.1%であった。また 26 過間の長期オランザビン対照試験では，EPS の発現率はアリビプラゾール群で 16.8％，オランザビン群で 15.7％であった。

通常の臨床検査項目で臨床的に意義のあると考えられる変動を示した患者の割合を，アリビプラゾール群とブラセボ群で比較したところ医学的に重要な差は認められなかった。概して一過性で無症候性の CPK（クレアチニンフォスホキナーゼ）の上昇は，ブラセボ群の 3.6%に対して，アリビプラゾール群では 3.9%に観察された。

**その他の所見：**
抗精神病療法に関連することが知られており，アリビプラゾール投与中に報告された副作用には，悪性症候群，遲発性ジスキネジア，痙攣，痙攣の高齢患者における脳血管性の有害事象，及び高血糖・糖尿病が含まれる（4.4 参照）。

**市販後調査：**
市販後調査の期間中下記の有害事象も稀に報告された（発生頻度の算出は推定投与患者数に基づくものである）：
免疫系障害：アレルギー反応（例えば、アナフィラキシー反応、血管浮腫、そう痒症、
或いは蕁麻疹 ）
精神障害 ： 神経過敏、激越
神経系障害 ： 会話障害
血管障害 ： 失神
胃腸障害 ： 唾液分泌亢進、脹炎
筋骨格系、結合組織および骨障害：こわばり感、筋痛、横紋筋融解
全身障害および投与局所様態：胸痛
臨床検査 ： クレアチンホスホキナーゼ増加、アラニン・アミノトランスフェラーゼ
増加（ALT）、アスパラギン酸アミノトランスフェラーゼ（AST）増加

4.9 過量投与
臨床試験において、推定最高用量 1080mg までのアリビブラゾールを偶発的又は企図的に
急性過量投与された患者が確認されているが、死亡例はなかった。アリビブラゾール
の過量投与後に観察された徵候・症状として、悪心、嘔吐、無力症、下痢、傾眠が報告
されている。

市販後自発報告の中で、最高 450mg までのアリビブラゾール単剤を過量投与された成人
患者において観察された徵候・症状として、頻脈、嘔吐が報告されている。さらに、こ
れまでに受領した小児に対するアリビブラゾール偶発的過量投与（195mg まで）の報告
で、医学的に重篤なる恐れのある徵候・症状として、錐体外路症状及び一過性の意識
消失が認められている。

最高で、アリビブラゾールを 140mg、1 日間投与された成人が少数例あったが、予測さ
れない有害事象は発現しなかった。また、90mg/日までを 15 日間投与した臨床試験におい
て、予測されない有害事象の発現は認められなかった。

過量投与の管理としては、補助療法、適切な気道確保、酸素吸人と換気及び症状管理に
集中すること。複数の薬剤が関与している可能性を考慮すること。従って、不整脈の発
現を検出するための継続した心電図モニタリングも含む心血管モニタリングを即座に開
始すること。アリビブラゾールの過量投与が確認された場合或いは疑われる場合は、患
者が回復するまで医学的な管理と監視を続けること。

アリビブラゾール投与 1 時間後の活性炭 (50g) 投与によりアリビブラゾールの Cmax は約
41%、AUC は約 51% 減少した。このことは活性炭が過量投与の治療に有効である可能性
を示している。

アリビブラゾール過量投与の治療における血液透析の効果に関する情報はないが、アリ
ビブラゾールが血漿蛋白に高度に結合することから、血液透析は過量投与の管理には有
用でないと考えられる。
5. 薬理学的特性
5.1 薬効薬理

薬物療法的分類：抗精神病薬，ATCコード；N05 AX12

アリピプラゾールの統合失調症に対する有効性は，ドバミン D₂及びセロトニン 5-HT₁A受容体に対する部分アゴニスト活性と，セロトニン 5-HT₂受容体に対するアンタゴニスト活性の両方を介して効果が発揮されるものと推定されている。アリピプラゾールは，ドバミン機能亢進の動物モデルにおいてアントゴニスト作用を，またドバミン機能低下の動物モデルにおいてアゴニスト作用を示した。アリピプラゾールは in vitro でドバミン D₂及び D₃，セロトニン 5-HT₁A及び 5-HT₂A受容体に対し高い親和性，ドバミン D₄，セロトニン 5-HT₂C及び 5-HT₇，DA 及びアドレナリン及びヒスタミン H₁受容体に対し中等度の親和性を示した。また，セロトニン再取り込み部位に中等度の親和性を示したが，ムスカリン受容体への親和性は認められなかった。その他の臨床的な効果についてはドバミン及びセロトニンのサブタイプ以外の受容体との相互作用により説明できるものもあるかもしれない。

健康人にアリピプラゾール 0.5〜30mg を一日一回，2 週間投与すると，D₂受容体リガンドである [¹²C]ラクロプライドの尾状核及び被膜への結合が用量に依存して低下することが陽電子放出断層撮影法によって確認された。

臨床試験に関するその他の情報：

統合失調症：陽性及び陰性症状のある統合失調症患者 1,228 例を対象とした 3 つの短期プラセボ対照試験（4〜6 週間）において，アリピプラゾールはプラセボと比較して，統計的に有意な精神病症状の改善を示した。

ABIILIFY は，初回投与で効果のあった患者の維持療法において，臨床症状の改善維持に効果がある。ハロペリドールとの比較対照試験において，投与 52 週目で効果が維持されたレスポンダーの割合は，両投与群で同様であった（アリピプラゾール群 77％，ハロペリドール群 73％）。全体の試験終了者の割合は，アリピプラゾール群（43％）が，ハロペリドール群（30％）より有意に高かった。副次的評価項目として用いられた，陽性・陰性症状評価尺度（PANSS）及び Montgomery Asberg うつ評価尺度（MADRS）を含む評価尺度における実際のスコアは，アリピプラゾール群がハロペリドール群に比べ有意に高い改善を示した。

慢性統合失調症で症状の安定している患者を対象とした 26 週間のプラセボ対照試験において，アリピプラゾール群の再発率は 34％と，プラセボ群の 57％に比べて有意に低かった。

体重増加：臨床試験において，アリピプラゾールは臨床的に意義のある体重増加を惹起させなかった。統合失調症患者 314 例における主要評価項目を体重増加とした，26 週間のオランザピン対照，二重盲検，多国間共同試験において，ベースラインより体重が少
なくとも 7%増加（例，投与前平均体重が 80.5kg で少なくとも 5.6kg の増加）した患者数は，オランザピン群（N=45，又は評価可能な患者の 33%）に比べてアリビプラゾール群（N=18，又は評価可能な患者の 13%）で有意に少なかった。

5.2 藥物動態

吸収：
アリビプラゾールの吸収は良好で，投与後 3～5 時間以内に最高血漿中濃度に達する。アリビプラゾールの初回通過効果は極めて少ない。錠剤を経口投与した際の絶対的生物学的利用率は 87%であった。高脂肪食はアリビプラゾールの薬物動態に影響しない。

分布：
アリビプラゾールは全身に広く分布し，みかけの分布容積 4.9 L/kg と，血管外への広範な分布を示している。治療濃度ではアリビプラゾールとデヒドロアリビプラゾールの 99%以上が血清蛋白，主としてアルブミンに結合している。

代謝：
アリビプラゾールは主として脱水素化，水酸化，N-脱アルキル化の 3 種の代謝経路により主として肝臓で大部分が代謝される。in vitro 試験では，CYP3A4 及び CYP2D6 により脱水素化及び水酸化され，CYP3A4 により N-脱アルキル化される。全身循環血液中では主としてアリビプラゾールが検出される。定常状態では血漿中 AUC の約 40%が活性代謝物デヒドロアリビプラゾールであった。

排泄：
経口投与後のアリビプラゾールの平均消失半減期は，CYP2D6 の extensive metabolizer で約 75 時間，CYP2D6 の poor metabolizer で約 146 時間である。

アリビプラゾールの全身クリアランスは 0.7mL/min/kg で，主に肝臓による。

[14C] で標識したアリビプラゾールを単回経口投与した場合，投与された放射活性の約 27%が尿中に，約 60%が糞中に回収された。尿中に排泄された未変化体は投与量の 1%未満，糞中から回収された未変化体は約 18%であった。

特殊患者群における薬物動態

高齢者：
健康な高齢者と若年成人間でアリビプラゾールの薬物動態に差は認められず，統合失調症患者のポピュレーションファーマコキネティックス解析においても，年齢による影響は認められなかった。

性別：
健康的男女間でアリビプラゾールの薬物動態に差は認められず、統合失調症患者のポビュレーションファーマコキネティックス解析においても、性別による影響は認められなかった。

喫煙状況及び人種:
ポビュレーションファーマコキネティックス解析において、アリビプラゾールの薬物動態に人種に関連した臨床的に意義のある差、或いは喫煙による影響は認められなかった。

腎疾患:
重度の腎障害患者と健康な若年成人におけるアリビプラゾールとデヒドロアリビプラゾールの薬物動態特性は、類似することが認められた。

肝疾患:
種々の程度の肝硬変（Child-Pugh 分類のクラス A，B 及び C）患者に対する単回投与試験において、肝障害はアリビプラゾール及びデヒドロアリビプラゾールの薬物動態に有意な影響を及ぼさなかった。しかし試験にはクラス C 肝硬変患者3例しか含まれておらず、代謝能に関する結論を出すには不十分である。

5.3 非臨床安全性
通常の安全性薬理試験、反復投与毒性試験、遺伝毒性、がん原性及び生殖発生毒性試験では、臨床において特記すべき有害事象の発現を示唆する成績は認められなかった。

毒性作用は、ヒトへの最高推奨用量 [MRHD] 或いは同用量投与時の曝露量と比べて著しく高用量を投与した場合或いは高曝露量の場合に認められ、臨床において発現する可能性が低いことが示されている。毒性作用として、20～60mg/kg/日（MRHD 投与時のヒトにおける定常状態の平均曝露量（AUC）との比較で 3～14 倍に相当）を 104 週間投与したラットにおける、用量に依存した副腎皮質所見（リポフスチンの累積及び/又は実質細胞消失）、及び 60mg/kg/日（MRHD 投与時のヒトにおける定常状態の平均曝露量（AUC）との比較で 14 倍に相当）を投与したメスのラットにおける副腎皮質腺癌の発現率、及び副腎皮質腫及び腺癌を合わせた発現率の増加が含まれる。
また、アリビプラゾール 25～125mg/kg/日（MRHD 投与時の定常状態の平均曝露量（AUC）との比較で 1～3 倍、或いは mg/m²換算でヒトにおける MRHD の 16～81 倍に相当）を反復経口投与後、サルの胆汁中においてアリビプラゾールのヒドロキシ代謝物の硫酸抱合体が沈殿した結果として、胆石症も認められた。しかし、ヒトにおいては MRHD である 30mg/日を投与した場合でも、胆汁中のヒドロキシ代謝物の硫酸抱合体濃度は、39 週間の試験においてサルで認められた胆汁内濃度の 6%以下であり、ヒト胆汁中における溶解度（6%）に比べて十分に低い濃度であった。
一連の遺伝毒性試験の結果から、アリビブラゾールに遺伝毒性はないと考えられた。生殖発生毒性試験では、アリビブラゾールは受胎能を障害しなかった。用量に依存する胎児の骨化の遅れや催奇形性の可能性を含む発生毒性が、治療量以下（AUC に基づく）を投与されたラット、及び MRHD 投与時の定常状態の平均 AUC の 3〜11 倍に相当する用量を投与されたウサギにおいて観察された。なお、これらの発生毒性を誘発した用量とほぼ同量を投与した母動物には毒性がみられた。

6. 薬剤特性

6.1 添 加 物 の リ ス ト

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Indigo carmine E132 aluminium lake

6.2 配合禁忌

なし

6.3 使用期限

2年間
6.4 貯法上の留意点

湿気を避けるため、元の包装のまま保管すること。

6.5 包装

ABILIFY 錠は、ミシン目入りのアルミニウムブリスター包装。
1箱：14、28、49、56、98 錠。
上記のサイズすべては市販されない可能性あり。

6.6 使用及び取扱い上の注意

特になし

7. 販売承認取得者

Otsuka Pharmaceutical Europe Ltd.
Commonwealth House, 2 Chalkhill Road
Hammersmith-London W6 8DW-United Kingdom

8. 販売承認番号

EU/1/04/276/001-005

9. 初回承認日/承認更新日

2023年 月 日

10. 改訂日
企業中核安全性情報（pytest）
COMPANY CORE SAFETY INFORMATION

ARIPIPRAZOLE
1.7 同種同効品一覧表

本薬と同一の効能・効果を有する抗精神病薬として、比較試験で対照薬としたハロぺリドール（1977年9月29日承認）、塩酸モサプラミン（1991年1月18日承認）及び本薬と同様に非定型抗精神病薬に分類される塩酸ペロスピロン（2000年12月22日承認）、オランザピン（2000年12月12日承認）、フマル酸クエチアピン（2000年12月12日承認）及びリスペリドン（1996年4月16日承認）を同種同効品一覧表に記載した（表1.7-1～1.7-4）。
### 表 1.7-1 同種・同効品一覧表（1）

<table>
<thead>
<tr>
<th>一般的名称</th>
<th>アリビラゾール</th>
<th>ハロベリドール</th>
</tr>
</thead>
<tbody>
<tr>
<td>販売名</td>
<td>エビリファイ錠 3mg, エビリファイ錠 6mg, エビリファイ散 1%</td>
<td></td>
</tr>
<tr>
<td>会社名</td>
<td>製造販売元：大塚製薬株式会社</td>
<td></td>
</tr>
<tr>
<td>承認年月日</td>
<td></td>
<td></td>
</tr>
<tr>
<td>再評価年月</td>
<td></td>
<td></td>
</tr>
<tr>
<td>規格区分</td>
<td>医薬、指定医薬品、処方箋医薬品</td>
<td></td>
</tr>
<tr>
<td>化学構造式</td>
<td><img src="image" alt="化学構造式" /></td>
<td></td>
</tr>
</tbody>
</table>

#### 藥剤・薬量

<table>
<thead>
<tr>
<th>藥剤・薬量</th>
<th>アリビラゾール</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mg</td>
<td>1錠中アリビラゾール 3mg, 総 6mg; 1錠中アリビラゾール 6mg</td>
</tr>
<tr>
<td>散 1%</td>
<td>1g中アリビラゾール 10mg</td>
</tr>
</tbody>
</table>

#### 効能又は効果

統合失調症

#### 用法及び用量

通常、成人にはアリビラゾールとして 1 日 6～12mg を開始用量、1 日 6～24mg を維持用量とし、1 回又は 2 回に分けて経口投与する。なお、年齢、症状により適宜増減するが、1 日量は 30mg を超えないこと。

#### 用法・用量に関連する使用上の注意

1. 本剤が定常状態に達するまでに約 2 週間を要するため、2 週間以内に増量しないことが望ましい。（薬物動向の参考）
2. 本剤の投与量は必要最小限となるよう、患者ごとに慎重に観察しながら調節すること。
3. 他の抗精神薬か本剤に変更する患者よりも、新たに統合失調症の治療を開始する患者で副作用が発現やすいため、このような患者ではより慎重に症状を観察しながら用量を調節すること。

### 禁忌

(1) 頭痛、顔色異常、皮膚炎、体重減少、栄養障害、心電図異常、心電図異常

(2) 本剤の成分に対し過敏症の既往歴のある患者

(3) 本剤の成分に対し過敏症の既往歴のある患者

(4) 本剤の成分に対し過敏症の既往歴のある患者

(5) 本剤の成分に対し過敏症の既往歴のある患者
表 1.7-1 同種・同効品一覧表（2）

<table>
<thead>
<tr>
<th>使用上の注意</th>
<th>慎重投与</th>
<th>一般的名称</th>
<th>ハロベリドール</th>
</tr>
</thead>
<tbody>
<tr>
<td>慎重投与</td>
<td>1. 慎重投与（次の患者には慎重に投与すること）</td>
<td>アリビラゾール</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) 肝障害のある患者 [肝障害を悪化させるおそれがある。]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2) 心・血管疾患、低血圧又はその他の危険のある患者 [一過性の血圧下降があらわれるおそれがあ る。]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) てんかん等の神経性疾患又はこれらの既往歴のある患者 [発作を誘発するおそれがある。]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4) 糖尿病及びその既往歴を有する患者、あるいは糖尿病の家族歴、高血圧、肥満等の糖尿病の危 険因子を有する患者（高糖値が上昇することがある。）（2. 重要な基本的注意(4)，(6)）の項及 び「4. 副作用（1）重大な副作用6 糖尿病性ケトアンドーシス、糖尿病性盲れ」の項参照）</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5) 自覚的に既往及び自覚念を有する患者 [症状を悪化させるおそれがある。]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6) 高齢者（5. 高齢者への投与）の項参照</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. 重要な基本的注意

(1) 監督、注意力・集中力・反射運動機能等の低下があるので、本剤投与中の患者には自動車の運転等危険な状態を伴う機械の操作に従事させないよう注意すること。

(2) 前治療薬からの切り替え時、興奮、抵抗、適性等の精神症状が悪化する場合があるので、観察を十分に行い、前治療薬の用量を徐々に減らしつつ、本剤の投与を行うことが望ましい。なお、悪化が見られた場合は他の機械用法に切り替えなる処置を行うことをねらうこと。

(3) 急性に不安、焦燥、興奮の症状を見ている患者に対し、本剤投与にて十分な効果が認められない場合には、静脈内投与等、他の対処方法も考慮すること。

(4) 非定型上気性神経症が投与されている患者において高血圧の報告があり、一部にはケトアンドーシス、高血圧性脳症を伴う顕著な症例、あるいは死亡に至る症例も報告されている。本剤投与中、年齢、年齢、年齢、年齢、年齢の高血圧の家族歴、高血圧、肥満等の糖尿病の危険因子を有する 患者については、血圧値の測定等の観察を十分に行うこと。（1. 慎重投与(4)の項及び「4. 副作用（1）重大な副作用6 糖尿病性ケトアンドーシス、糖尿病性盲れ」の項参照）

(5) 本剤の投与に関し、あらかじめ上記(3)の副作用が発現する場合があることを、患者及びその家族に十分に説明し、年齢、年齢、年齢、年齢、年齢の注意を各皮膚科等の院内に注意を示すので、このような症状があらわれた場合には、直ちに投与中止し、医師の診断を受けるよう指導すること。（1. 慎重投与(4)の項及び「4. 副作用（1）重大な副作用6 糖尿病性ケトアンドーシス、糖尿病性盲れ」の項参照）

(6) 体液減少があらわれた場合には、糖尿病の発症・増悪、悪性腫瘍の発症等の合併症も考えられ るため、経過を慎重に観察し、体液減少の原因を究明し、適切な処置を行うこと。

(7) 他の抗精神薬剤を既に投与しているなど血清プロラクチン濃度が高い場合に本剤を投与する と、血清プロラクチン濃度が低下し月経周期が再開することがあるので、月経周期、質、子宮 内膜症などの発症に十分注意すること。

(8) 社会学的・社会的リスクのある患者に本剤を投与する場合には、慎重に経過を観察すること。
### 表 1.7-1 同種・同効品一覧表（3）

<table>
<thead>
<tr>
<th>使用上の注意</th>
<th>アリピラゾール</th>
<th>ハロベリドール</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>相互作用</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7  同種同効品一覧表</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 3. 相互作用

**本剤は、主として肝代謝酵素 CYP3A4 及び CYP2D6 で代謝される。**

（薬物動態）の項参照

（1）併用禁忌（併用しないこと）

<table>
<thead>
<tr>
<th>薬剤名等</th>
<th>動態状況・置換方法</th>
<th>機作・効能因子</th>
</tr>
</thead>
<tbody>
<tr>
<td>エピネフリン</td>
<td>エピネフリンの作用を消去させ、血圧低下を起こすおそれがある。</td>
<td>機作・効能因子</td>
</tr>
</tbody>
</table>

エピネフリンはアドレナリン作用性。交感神経の制御系である。本剤の作用は、血圧を降下させることができる。検査・投薬を行う。

#### 2. 併用注意（併用に注意すること）

<table>
<thead>
<tr>
<th>薬剤名等</th>
<th>動態状況・置換方法</th>
<th>機作・効能因子</th>
</tr>
</thead>
<tbody>
<tr>
<td>高血圧剤</td>
<td>相互に降圧作用を増強することがあるので、降圧するなど併用により血圧を増加させる。</td>
<td>機作・効能因子</td>
</tr>
<tr>
<td>抗コリン作用有する薬剤</td>
<td>抗コリン作用を増強させることができるので、降圧するなど併用により血圧を増加させる。</td>
<td>機作・効能因子</td>
</tr>
<tr>
<td>ドバミン作用薬</td>
<td>ドバミン作用作用を減弱するおそれがあるので、投与量を調整するなど併用により血圧を増加させる。</td>
<td>機作・効能因子</td>
</tr>
<tr>
<td>アルコール（飲酒）</td>
<td>相互に降圧作用を増強させることができるので、降圧するなど併用により血圧を増加させる。</td>
<td>機作・効能因子</td>
</tr>
<tr>
<td>CYP2D6 阻害作用有する薬剤</td>
<td>本剤の作用が増強するおそれがあるので、本剤を減量するなど考慮すること。</td>
<td>機作・効能因子</td>
</tr>
<tr>
<td>キリン等</td>
<td>本剤の主要代謝酵素である CYP2D6 を阻害するため血液中濃度が上昇するおそれがある。（薬物動態）の項参照</td>
<td></td>
</tr>
<tr>
<td>CYP3A 阻害作用有する薬剤</td>
<td>本剤の作用が増強するおそれがあるので、本剤を減量するなど考慮すること。</td>
<td>機作・効能因子</td>
</tr>
<tr>
<td>イトコナゾール、カテーテル等</td>
<td>本剤の主要代謝酵素である CYP3A を阻害するため血液中濃度が上昇するおそれがある。（薬物動態）の項参照</td>
<td></td>
</tr>
<tr>
<td>本剤の薬効作用有する薬剤</td>
<td>本剤の薬効作用有する薬剤は、血液中濃度が低下するおそれがある。（薬物動態）の項参照</td>
<td></td>
</tr>
<tr>
<td>カルパノゼピン等</td>
<td>本剤の薬効作用有する薬剤は、血液中濃度が低下するおそれがある。（薬物動態）の項参照</td>
<td></td>
</tr>
</tbody>
</table>
表 1.7-1 同種・同効品一覧表（4）

<table>
<thead>
<tr>
<th>一般的称名</th>
<th>アリビラゾール</th>
<th>ハロペリドール</th>
</tr>
</thead>
<tbody>
<tr>
<td>使用上の注意</td>
<td>4. 副作用</td>
<td></td>
</tr>
<tr>
<td></td>
<td>国内臨床試験において安全性解析の対象となった743例中、副作用が452例（60.8％）に認められた。主な副作用は、不眠（27.1％）、神経障害（14.8％）、アカジア（11.7％）、指感（手指振戦等）（10.5％）、不安（9.6％）、体重減少（9.2％）、筋弛緩（6.3％）及び食欲不振（6.2％）であった。また、主な臨床検査の異常変動はCK（CPK）上昇（13.7％）、プロラクチン低下（10.9％）及びALT（GPT）上昇（7.0％）であった。</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) 重大な副作用</td>
<td></td>
</tr>
<tr>
<td></td>
<td>悪性症候群（Syndrome malin）（0.3％）</td>
<td></td>
</tr>
<tr>
<td></td>
<td>僕動減弱、強度の筋弛緩、嘔下困難、腹膨、血圧の変動、発汗等が観察し、それにひきつづき発熱がみられる場合は、投与を中止し、体冷却、水分補給等の全身管理とともに適切な処置を行うこと。本症発症時には、白血球の増加や血液CK（CPK）の上昇がみられることが多いため、ミオグロビン尿を伴う腎機能低下がみられることがある。</td>
<td></td>
</tr>
<tr>
<td></td>
<td>噘発症（1.1％）</td>
<td></td>
</tr>
<tr>
<td></td>
<td>長期投与により、口渋部等の不随意運動があらわれることがあるが、このような症状があらわれた場合は減量又中止を考慮すること。なお、投与中止後も症状が持続することがある。</td>
<td></td>
</tr>
<tr>
<td></td>
<td>噘発症（0.3％）</td>
<td></td>
</tr>
<tr>
<td></td>
<td>指端静脈炎（食事断端、腸内不整、腹部の酯酸あるいは結腸及び腸内容物のとどろい等の症状）をきたし、頑発症性リイスに移行することがあるので、嘔管麻痺があらわれた場合には、投与を中止すること。</td>
<td></td>
</tr>
<tr>
<td></td>
<td>アナフィラキシー様症状</td>
<td></td>
</tr>
<tr>
<td></td>
<td>アナフィラキシー様症状が現れることはあるが、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。</td>
<td></td>
</tr>
<tr>
<td></td>
<td>様数筋麻痺</td>
<td></td>
</tr>
<tr>
<td></td>
<td>妊娠期薬剤治療があらわれることがあるので、CK（CPK）上昇、血中および尿中ミオグロビン上昇等に注意すること。</td>
<td></td>
</tr>
<tr>
<td></td>
<td>糖尿病性ケトアシドーシス</td>
<td></td>
</tr>
<tr>
<td></td>
<td>糖尿病性ケトアシドーシス susceptible、糖尿病性昏迷</td>
<td></td>
</tr>
<tr>
<td></td>
<td>糖尿病性ケトアシドーシス、糖尿病性昏迷から死亡に至るなどの致命的な経過をたどった症例が報告されているので、本剤投与中は多量、多頻、多食、脱力感等の症状の発現に注意すること。更に症状の発現を十分に観察を行い、異常が認められた場合には、インスリン投与の投与等の適切な処置を行うこと。</td>
<td></td>
</tr>
</tbody>
</table>

注1 外国における臨床試験において報告（0.4％）がある。
注2 外国において販売後自発報告（頻度不明）がある。
<table>
<thead>
<tr>
<th>副作用</th>
<th>一般的名称</th>
<th>アリビラゾール</th>
<th>ハロベリドール</th>
</tr>
</thead>
<tbody>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2）その他の副作用</td>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 表 1.7-1 同種・同効品一覧表（6）

<table>
<thead>
<tr>
<th>一般的名称</th>
<th>アリビプラゾール</th>
<th>ハロベリドール</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10％以上</td>
<td>1〜10％</td>
</tr>
<tr>
<td>精神神経系</td>
<td>頭痛*，眠気*</td>
<td>頭痛，眠気，ふるふる震え</td>
</tr>
<tr>
<td>腦体外障症状</td>
<td>アカジア*，振戦*，振戦外障</td>
<td>異常運動，パーキンソン様症状，ジスキネジア</td>
</tr>
<tr>
<td>消化器</td>
<td>食心*，消化不良*，嘔吐*，発熱*</td>
<td>濡病，CK（CPK）上昇</td>
</tr>
<tr>
<td>肝臓</td>
<td>ALT（GPT）上昇，AST（GOT）上昇，γ-GTP</td>
<td>上昇</td>
</tr>
<tr>
<td>過敏症</td>
<td>アレルギー反応，血管浮腫，そう痒症，蕁麻疹</td>
<td></td>
</tr>
<tr>
<td>代謝異常</td>
<td>糖尿病，CK（CPK）上昇</td>
<td></td>
</tr>
<tr>
<td>その他</td>
<td>脱力感*，顔面*</td>
<td>発熱，痛広浸</td>
</tr>
</tbody>
</table>

注）a）統合失調症に対するブレセボ対照試験において報告された有害事象でアリビプラゾール群（879例）とブレセボ群（866例）の発現率の差が1％以上であったもの 
b）ブレセボ群との発現率の差は1％未満であるが，臨床的に重要と判断されたもの 
c）自発報告において認められた副作用のため発見例不明

### 1.7 同種・同効品一覧表

5. 高齢者への投与

一般に高齢者では生理機能が低下しているので，患者の状態を観察しながら慎重に投与すること。

### 使用上の注意

| 妊婦・産婦，授乳婦等への投与 |
|-----------------|-----------------|
| 付) 妊婦又は妊娠している可能性のある婦人には，治療上の有益性が危険性を上回ると判断される場合にのみ投与すること（妊娠中の中枢の投与に関する安全性は確立していない） |
| (2) 授乳中の婦人に投与する場合には，授乳を中止せること（動物実験ラット）で乳汁移行が報告されている |

### 小児等への投与

<table>
<thead>
<tr>
<th>小児等への投与</th>
</tr>
</thead>
<tbody>
<tr>
<td>妊出乳児，新生児，乳児，幼児又は小児に対する安全性は確立していない（使用経験がない）</td>
</tr>
</tbody>
</table>
### 表 1.7-1 同種・同効品一覧表（7）

<table>
<thead>
<tr>
<th>一般的名称</th>
<th>アリビブラゾール</th>
<th>ハロベリドール</th>
</tr>
</thead>
<tbody>
<tr>
<td>用量投与</td>
<td>8. 用量投与</td>
<td>頻度、症状：</td>
</tr>
<tr>
<td></td>
<td></td>
<td>本剤を過量投与した報告は少ない。外観臨床試験において最高 1080mg までの急性過量投与が報告されているが、死亡はないと。用量投与の症状として潛伏、嘔吐、悪心、下痢、顕微鏡が報告されている。外観の販売後報告において、1200mg まで服用した成人で嘔吐、発汗、血圧上昇、脈拍、嘔吐、塩酸的 195mg まで服用した投与で一過性の意識消失が発現した。</td>
</tr>
<tr>
<td></td>
<td></td>
<td>処置：</td>
</tr>
<tr>
<td></td>
<td></td>
<td>特異的解毒剤は知られていない。本剤を過量に服用した場合は、補助療法、気道確保、酸素吸入、換気及び症状管理に集中すること。心中動脈のモニターを開始し、心電図で不整脈の発現を継続的にモニターしながら患者が安定するまで十分に観察すること。活性剤の早期投与は有用である。血液透析是有用でないと考えられる。なお、他の副作用の可能性を考えられる場合はその影響に留意すること。</td>
</tr>
<tr>
<td>通用上の注意</td>
<td>通用上の注意</td>
<td>疫薬交付時：P.T.P 包装の薬剤は P.T.P シートから取り出して服用するよう指導すること。[P.T.P シートの取扱いにより、硬い観音部が食道粘膜へ刺入し、更には穿孔を起こして細菌感染等の重篤な合併症を併発することが報告されている。]</td>
</tr>
<tr>
<td>その他の注意</td>
<td>その他の注意</td>
<td>(1) 本剤による治療中原因不明の突然死が報告されている。</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) げっ歯類（マウス、ラット）のすなは原性試験において、乳鉢投与（マウス 3mg/kg/日以上、ラット 10mg/kg/日）及び下垂体投与（マウス 3mg/kg/日以上）の発生頻度の上昇が報告されている。これらの投与はげっ歯類では血中プロラクチンの上昇と關連した変化としてよく知られている。ラットのすなは原性試験において、60mg/kg/日（最終非処置用原形の 100 倍に相当）のすなが投与群で腎炎及び胃粘膜の発生頻度の上昇が報告されている。</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) サルの反復投与試験において顕のみの漬汁（桑液、桜の芽）、ある 3 週間～52 週間試験の 25mg/kg/日以上の用量で、肝腎に尿素の肝機能検査値の上昇が見られた。9 週間試験の 50mg/kg/日以上の用量で報告されている。汁は本剤の使用に伴う代謝物がサル培養中で測定される濃度を越える濃度となり測定したものと考えられた。なお、これら代謝物のサル肝汁中における濃度（1日 15 mg/kg 授与、その後 6 日間 30mg/kg 反復投与) はサル肝汁中における濃度の 56%以下であり、また、他のサル肝汁中における測定値が 5.4%以下であった。</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4) 外国で実施された認知症に関連した精神病症状（神経外皮質効果）を有する高齢患者を対象とした 17 の臨床試験において、本剤を含む判定型精神病薬投与群はプラセボ投与群と比較して、死亡率が 1.6～1.7 倍高かったとの報告がある。死因は様々であったが、心血管系（心不全、突然死など）又は感染症（肺炎など）による死亡が多かった。なお、本剤の 3 試験（計 938 例、平均年齢 82.4 歳；56～99 歳）では、死亡及び脳血管障害（脳卒中、一過性脳虚血発作等）の発現率がプラセボと比較して高かった。</td>
</tr>
<tr>
<td>備考</td>
<td>部会提出版</td>
<td></td>
</tr>
<tr>
<td>一般的名称</td>
<td>塩酸モサブラミン</td>
<td>盐酸ヘロスピロン</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>一般販売名</td>
<td></td>
<td></td>
</tr>
<tr>
<td>会社名</td>
<td></td>
<td></td>
</tr>
<tr>
<td>承認年月日</td>
<td></td>
<td></td>
</tr>
<tr>
<td>再審査年月</td>
<td></td>
<td></td>
</tr>
<tr>
<td>国別区分</td>
<td></td>
<td></td>
</tr>
<tr>
<td>化学構造式</td>
<td></td>
<td></td>
</tr>
<tr>
<td>処方・製造</td>
<td></td>
<td></td>
</tr>
<tr>
<td>効能又は効果</td>
<td></td>
<td></td>
</tr>
<tr>
<td>用法及び用量</td>
<td></td>
<td></td>
</tr>
<tr>
<td>禁忌</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.7 同種同効品一覧表
<table>
<thead>
<tr>
<th>一般的名称</th>
<th>塩酸モプラミン</th>
<th>塩酸ベロスピロン</th>
</tr>
</thead>
<tbody>
<tr>
<td>使用上の注意</td>
<td>重要な基本的注意</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>相互作用</td>
<td></td>
<td></td>
</tr>
<tr>
<td>一般の名称</td>
<td>塩酸モサプラミン</td>
<td>塩酸ベロスピロン</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>副作用</td>
<td></td>
<td></td>
</tr>
<tr>
<td>一般的名称</td>
<td>塩酸モサプラミン</td>
<td>塩酸ヒロスビロン</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>使用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>副作用</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
表 1.7-2 同種・同効品一覧表(5)

<table>
<thead>
<tr>
<th>使用上の注意</th>
<th>塩酸モサプラミン</th>
<th>塩酸ヘロスピロン</th>
</tr>
</thead>
<tbody>
<tr>
<td>高齢者への投与</td>
<td></td>
<td></td>
</tr>
<tr>
<td>妊娠、産婦、授乳婦等への投与</td>
<td></td>
<td></td>
</tr>
<tr>
<td>小児等への投与</td>
<td></td>
<td></td>
</tr>
<tr>
<td>適量投与</td>
<td></td>
<td></td>
</tr>
<tr>
<td>適用上の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>その他の注意</td>
<td></td>
<td></td>
</tr>
<tr>
<td>備考</td>
<td></td>
<td></td>
</tr>
<tr>
<td>一般の名称</td>
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| 使用上の注意 | オランザピン | フマル酸クエン酸ビン
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表 1.7-3 同種・同効品一覧表(5)

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<td>小児等への投与</td>
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1.7 同種同効品一覧表

20
表 1.7-4 同種・同効品一覧表(2)

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表 1.7-4 同種・同効品一覧表(3)

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表 1.7-4 同種・同効品一覧表(4)

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表 1.7-4 同種・同効品一覧表 (5)

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<td>高齢者への投与</td>
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<tr>
<td>妊婦・産婦授乳婦等への投与</td>
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