1. NAME OF THE MEDICINAL PRODUCT

Zalonil 10 mg orodispersible tablets
Zalonil 15 mg orodispersible tablets
Zalonil 30 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zalonil 10 mg orodispersible tablets
Each orodispersible tablet contains 10 mg of aripiprazole.
Excipient with known effect
1 mg aspartame (E 951) and 95.05 mg lactose per orodispersible tablet

Zalonil 15 mg orodispersible tablets
Each orodispersible tablet contains 15 mg of aripiprazole.
Excipient with known effect
1.5 mg aspartame (E 951) and 142.58 mg lactose per orodispersible tablet

Zalonil 30 mg orodispersible tablets
Each orodispersible tablet contains 30 mg of aripiprazole.
Excipient with known effect
3 mg aspartame (E 951) and 285.15 mg lactose per orodispersible tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Zalonil 10 mg orodispersible tablets
Round and pink, with the marking "10" on one side.

Zalonil 15 mg orodispersible tablets
Round and yellow, with the marking "15" on one side.

Zalonil 30 mg orodispersible tablets
Round and pink, with the marking "30" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zalonil is indicated for the treatment of schizophrenia in adults and adolescents aged 15 years and older.
Zalonil is indicated for the treatment of moderate to severe manic episode in bipolar I disorder and for the prevention of new manic episodes in adults who have predominantly experienced manic episodes and where the manic episode has responded to treatment with aripiprazole (see section 5.1).
Zalonil is indicated for the treatment of up to 12 weeks of moderate to severe manic episode in bipolar I disorder in adolescents 13 years of age and older (see section 5.1).

4.2 Posology and method of administration

Posology:

Adults

Schizophrenia: The recommended starting dose for Zalonil is 10 or 15 mg/day with a maintenance dose of 15 mg/day, given once a day and regardless of meals.
Zalonil is effective in the dose range of 10 to 30 mg/day. No increase in efficacy has been demonstrated at doses higher than the 15 mg daily dose, although some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes in Bipolar I Disorder: The recommended starting dose for Zalonil is 15 mg given once daily without regard to meals, as monotherapy or in combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Prevention of recurrence of manic episodes in bipolar I disorder: To prevent recurrence of manic episodes in patients receiving aripiprazole, alone or in combination therapy, treatment should be continued at the same dose. Daily dose adjustments, including dose reduction, should be considered based on the clinical situation.

Paediatric population:

Schizophrenia in adolescents 15 years of age and older: the recommended dose for Zalonil is 10 mg/day given on a once-a-day schedule, regardless of meals. Treatment should be started with 2 mg (using 1 mg/ml Zalonil oral solution) over 2 days, titrated to 5 mg for an additional 2 days to reach the recommended daily dose of 10 mg. Where appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

Zalonil is effective in a dose range of 10 to 30 mg/day. Increased efficacy has not been demonstrated at doses greater than a daily dose of 10 mg, although individual patients may benefit from a higher dose.
Zalonil is not recommended in patients with schizophrenia below the age of 15 years due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Manic Episodes in Bipolar I Disorder in Adolescents 13 Years of Age and Over: The recommended dose for Zalonil is 10 mg/day given on a once-a-day schedule, regardless of meals. Treatment should be initiated at 2 mg (using 1 mg/ml Zalonil oral solution) over 2 days, then titrated to 5 mg over 2 additional days to reach the recommended daily dose of 10 mg. The duration of treatment should be the minimum necessary to control symptoms and should not exceed 12 weeks. Increased efficacy has not been demonstrated with doses greater than a daily dose of 10 mg and a daily dose of 30 mg is associated with a significantly higher incidence of adverse reactions, including events related to extrapyramidal symptoms, drowsiness, fatigue and weight gain (see section 4.8). Doses greater than 10 mg/day should therefore be used only in exceptional cases and with careful clinical monitoring (see sections 4.4, 4.8 and 5.1). Younger patients are at higher risk for

aripiprazole-associated adverse events. In this regard, Zalonil is not recommended for use in patients below the age of 13 years (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: The safety and efficacy of Zalonil in children and adolescents below the age of 18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Tics associated with Tourette's Syndrome: The safety and efficacy of Zalonil in children and adolescents aged 6 to 18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Special populations:

Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, insufficient data are available to make recommendations. Administrations should be carefully controlled in these patients. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Renal impairment.
No dose adjustment is necessary for patients with renal impairment.

Elderly patients
The efficacy and safety of Zalonil in the treatment of schizophrenia or manic episodes in bipolar I disorder has not been established in patients aged 65 years and over. Due to the greater susceptibility of this population, a lower starting dose should be considered when justified by clinical factors (see section 4.4).

Sex
No dose adjustment is required for female patients compared to male patients (see section 5.2).

Smoking
In accordance with the metabolic pathway of aripiprazole, no dose adjustment is required for smokers (see section 4.5).

Dosage adjustments due to interactions
The aripiprazole dose should be reduced in case of concomitant administration of strong inhibitors of CYP3A4 or CYP2D6. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from combination therapy, the aripiprazole dose should then be increased (see section 4.5).
The dose of aripiprazole should be increased with concomitant administration of strong inducers of CYP3A4. When the CYP3A4 inducer is withdrawn from combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

Zalonil is for oral use.

The orodispersible tablet should be placed in the mouth, on the tongue, where it will quickly disperse in the saliva. It can be taken with or without liquids. Removal of the intact orodispersible tablet from the mouth is difficult. As the orodispersible tablet is fragile, it must be taken immediately after opening the blister. Alternatively, the tablet may be dispersed in water and the resulting suspension ingested.

Orodispersible tablets or oral solution can be used as an alternative to Zalonil tablets for patients who have difficulty swallowing Zalonil tablets (see also section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

During treatment with antipsychotics, it may take several days to a few weeks for the patient's clinical condition to improve. Patients should be carefully monitored throughout this period.

Suicide risk
The occurrence of suicidal behavior is inherent in psychotic illnesses and behavior disorders and, in some cases, has been reported soon after initiation of, or switching from, antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Treatment with antipsychotics of high-risk patients should be accompanied by careful supervision.

Cardiovascular disorders
Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction disturbance), cerebrovascular disease, conditions that predispose patients to hypotension (dehydration, hypovolaemia and treatment with antihypertensive drugs) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. As patients treated with antipsychotics often have acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures should be taken.

QT interval prolongation
In clinical trials of aripiprazole, the incidence of prolonged QT interval was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of prolonged QT interval (see section 4.8).

Tardive dyskinesia
In clinical trials of one year or less, during treatment with aripiprazole there were infrequent reports of treatment-emergent dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient receiving aripiprazole, dose reduction or discontinuation should be considered (see section 4.8). These symptoms may temporarily worsen, or may even appear, after stopping treatment.

Other extrapyramidal symptoms
Akathisia and parkinsonism were observed in clinical trials conducted in pediatric patients with aripiprazole. If symptoms and signs of other extrapyramidal effects occur in patients taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal set of symptoms associated with antipsychotics. In clinical trials, 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 arrhythmia). Additional signs may include elevation of creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevations in creatine phosphokinase and rhabdomyolysis, not necessarily associated with NMS, have been reported. If a patient develops signs and symptoms indicative of NMS, or develops unexplained high fever without additional clinical manifestations of NMS, all antipsychotics, including aripiprazole, should be discontinued.

Seizures
In clinical trials, infrequent cases of seizures were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients with a history of seizures or conditions associated with seizures (see section 4.8).

Elderly patients with dementia-related psychosis

Increase in mortality
In three placebo-controlled trials of aripiprazole (n = 938; mean age: 82.4 years; range: 56-99 years) in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The death rate in the aripiprazole-treated patients was 3.5% compared to 1.7% in the placebo group. Although the causes of death were varied, the majority of deaths appeared to be cardiovascular (eg heart failure, sudden death) or infectious (eg pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions
In the same trials, cerebrovascular adverse reactions (eg stroke, transient ischemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of patients treated with aripiprazole reported cerebrovascular adverse reactions in these trials, compared with 0.6% of patients treated with placebo. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose-response relationship to cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8).

Aripiprazole is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus
In patients treated with atypical antipsychotic medicinal products, including aripiprazole, hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported. Risk factors that

may predispose patients to serious complications include obesity and a family history of diabetes. In clinical trials with aripiprazole there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or abnormal blood glucose laboratory values compared to placebo. Precise estimates of the risk of hyperglycaemia-related adverse reactions in patients treated with aripiprazole and other atypical antipsychotics that allow direct comparisons are not available. Patients treated with any antipsychotics, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

Hypersensitivity
Hypersensitivity reactions with aripiprazole, characterized by allergic symptoms, may occur (see section 4.8).

Weight gain
Weight gain is often seen in schizophrenic patients with bipolar mania due to comorbidities, use of antipsychotics known to cause weight gain, unhealthy lifestyle, and which can lead to serious complications. Weight gain has been reported post-marketing in patients receiving aripiprazole. When observed, it is usually in patients with significant risk factors such as a history of diabetes, thyroid disease or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials in adolescent patients with bipolar mania, aripiprazole was shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If the weight gain is clinically relevant, a dose reduction should be considered (see section 4.8).

Dysphagia
Changes in esophageal motility and aspiration have been associated with the use of antipsychotics, including aripiprazole. Aripiprazole should be used with caution in patients at risk of aspiration pneumonia.

Pathological gambling and other impulse control disorders:

While taking aripiprazole, patients may experience increased urges, particularly for pathological gambling, and an inability to control these urges. Other urges that have been reported include: increased sex drive, compulsive shopping, binge eating, and other impulsive or compulsive behaviors. It is important for prescribers to ask patients or their caregivers about the development of new or increased urges from pathological gambling, sexual, compulsive shopping, binge eating or other urges while on aripiprazole treatment. It is important to note that impulse control symptoms may be associated with the underlying disease; however, in some cases, impulses have been reported to stop when the dose was reduced or the medication was discontinued. Impulse control disorders can harm the patient and others if not recognized. If a patient develops urges while taking aripiprazole, dose reduction or discontinuation of medication should be considered (see section 4.8).

Phenylketonuria
Zalonil orodispersible tablets contains aspartame, a source of phenylalanine that may be harmful to people with phenylketonuria.

Lactose
Zalonil tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Patients with comorbidity associated with attention deficit hyperactivity disorder (ADHD)
Despite the high frequency of comorbidity of bipolar I disorder and ADHD, the safety data available on the concomitant use of aripiprazole and other stimulants are very limited. Therefore, special care should be taken when these drugs are co-administered.

Falls
Aripiprazole can cause drowsiness, postural hypotension, and motor and sensory instability, which can lead to falls. Care should be taken when treating high risk patients and a lower starting dose should be considered (eg elderly or debilitated patients; see section 4.2).

4.5 Drug interactions and other forms of interaction

Aripiprazole has the potential to enhance the effect of certain antihypertensive drugs due to its α1-adrenergic receptor antagonism.
Given the primary CNS effects of aripiprazole, caution should be exercised when aripiprazole is administered in combination with alcohol or other CNS-acting medicinal products that have overlapping adverse reactions such as sedation (see section 4.8).
Caution should be exercised if aripiprazole is administered concomitantly with medicinal products known to cause prolonged QT interval or electrolyte imbalance.

Potential for other drugs to affect aripiprazole
A gastric acid blocker, the H2 antagonist famotidine, reduces the rate of absorption of aripiprazole, but this effect was not considered clinically relevant. Aripiprazole is metabolized by multiple pathways involving CYP2D6 and CYP3A4 enzymes, but not CYP1A enzymes. Consequently, no dose adjustment is necessary for smokers.

Quinidine and other CYP2D6 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while Cmax was unchanged. The AUC and Cmax of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. With concomitant administration of aripiprazole and quinidine, the dose of aripiprazole should be reduced to approximately half of the prescribed dose. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, can be expected to have similar effects and therefore similar dose reductions should be applied.

Ketoconazole and other CYP3A4 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and Cmax by 63% and 37%, respectively. The AUC and Cmax of dehydro-aripiprazole were increased by 77% and 43%, respectively. In CYP2D6 poor metabolizers, concomitant use of strong CYP3A4 inhibitors may result in higher aripiprazole plasma concentrations compared to CYP2D6 extensive metabolizers.

When considering co-administration of ketoconazole or other strong inhibitors of CYP3A4 with aripiprazole, the potential benefits must outweigh the potential risks to the patient. In the concomitant administration of ketoconazole with aripiprazole, the dose of aripiprazole should be reduced to approximately half of the prescribed dose. Other potent inhibitors of CYP3A4 such as itraconazole and HIV protease inhibitors can be expected to have similar effects and therefore similar dose reductions should be applied (see section 4.2).

After discontinuation of the CYP2D6 or CYP3A4 inhibitor, the aripiprazole dose should be increased to the value prior to initiation of concomitant therapy.

When weak inhibitors of CYP3A4 (eg diltiazem) or CYP2D6 (eg escitalopram) are used concomitantly with aripiprazole, small increases in aripiprazole plasma concentrations can be expected.

Carbamazepine and other CYP3A4 inducers
Following co-administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizophrenic disorder, the geometric mean Cmax and AUC for aripiprazole were 68% and 73% lower, respectively, compared to administration of aripiprazole (30 mg) as monotherapy. Similarly, for dehydro-aripiprazole, the geometric means of Cmax and AUC after co-administration of carbamazepine were 69% and 71% lower, respectively, than those obtained after treatment with aripiprazole alone.

The dose of aripiprazole should be doubled when aripiprazole is administered concomitantly with carbamazepine. Concomitant administration of aripiprazole and other CYP3A4 inducers (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St John's Wort) have similar effects and therefore similar dose increases should be applied. After discontinuation of strong inducers of CYP3A4, the aripiprazole dose should be reduced to the recommended dose.

Valproate and lithium
There were no clinically significant changes in aripiprazole concentrations when valproate or lithium were co-administered with aripiprazole, therefore no dose adjustment is required when valproate or lithium is administered with aripiprazole.

Potential for aripiprazole to affect other medications
In clinical studies, doses of 10-30 mg/day of aripiprazole had no significant effect on substrate metabolism of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole showed no potential to alter CYP1A2-mediated metabolism in vitro. Consequently, aripiprazole is unlikely to cause clinically important drug interactions mediated by these enzymes.
When aripiprazole was co-administered with valproate, lithium, or lamotrigine, there was no clinically important change in valproate, lithium, or lamotrigine concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital abnormalities have been reported; however, a causal relationship with aripiprazole could not be established. Animal studies cannot exclude potential developmental toxicity (see section 5.3). Patients must be advised to inform their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient information on human safety and concerns raised by animal reproduction studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.
Neonates exposed during the third trimester of pregnancy to antipsychotics (including aripiprazole) are at risk for adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration after administration. Agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disturbance have been reported. Consequently, neonates should be carefully monitored (see section 4.8).

Breastfeeding
Aripiprazole is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from aripiprazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Aripiprazole did not alter fertility, based on data from reproductive toxicity studies.

4.7 Effects on ability to drive and use machines
Aripiprazole has a limited to moderate effect on the ability to drive and use machines due to potential effects on the nervous system and vision, such as sedation, somnolence, syncope, blurred vision and diplopia (see section 4.8).

4.8 Undesirable effects
Security profile summary
The most frequently reported adverse reactions in placebo-controlled trials were akathisia and nausea, each occurring in more than 3% of patients treated with oral aripiprazole.

Tabular list of adverse reactions
The incidences of adverse drug reactions (ADRs) associated with aripiprazole therapy are shown in the table below. The table is based on adverse reaction events reported during clinical trials and/or post-marketing use.
All ADRs are listed by system organ classes and frequency; very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1.000, < 1/100), rare (≥ 1/10.000, < 1/1.000), very rare (< 1/10.000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
The frequency of adverse reactions reported during the post-marketing period cannot be determined as they derive from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "unknown".

	Common	Uncommon	Unknown

Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (eg anaphylactic reaction, angioedema including swollen tongue, tongue swelling, facial swelling, pruritus or urticaria)
Endocrine disorders		Hyperprolactinemia	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycemia	Hyponatremia Anorexia Decreased weight Weight gain
Psychiatric disorders	Insomnia Anxiety Restlessness	Depression Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Impulse control disorders Binge eating Compulsive shopping Poriomania Aggressiveness Agitation Nervousness
Nervous system disorders	akathisia extrapyramidal disorder tremor headache sedation Somnolence Dizziness	tardive dyskinesia dystonia	Neuroleptic Malignant Syndrome (NMS) tonic-clonic seizure serotonin syndrome speech disorder
Eye disorders	Blurred vision	diplopia Photophobia	oculogyric crisis
Cardiac disorders		Tachycardia	unexplained sudden death Torsades de pointes QT interval prolongation ventricular arrhythmias Heart attack bradycardia
Vascular disorders		Orthostatic Hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) hypotension Syncope
Respiratory, thoracic and mediastinal disorders		Hiccups	aspiration pneumonia laryngospasm oropharyngeal spasm

Gastrointestinal disorders	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhea Abdominal discomfort Stomach discomfort
Hepatobiliary disorders			Liver failure Hepatitis Jaundice Increased alanine aminotransferase (ALT) Increase in aspartate aminotransferase (AST) Increase in gamma-glutamyltransferase (GGT) Alkaline phosphatase increase
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Neonatal drug withdrawal syndrome (see section 4.6)
Reproductive system and breast disorders			Priapism

General disorders and administration site conditions	Fatigue		Temperature regulation disorder (eg, hypothermia, pyrexia) Chest pain Peripheral edema
Investigations			Increased blood glucose Increased glycosylated hemoglobin Blood glucose fluctuation Increase in creatine phosphokinase

Description of selected adverse reactions

Adults

Extrapyramidal symptoms (EPS)
Schizophrenia: In a 52-week long-term controlled trial, aripiprazole-treated patients had an overall (25.8%) lower incidence of EPS, including parkinsonism, akathisia, dystonia, and dyskinesia, compared with haloperidol-treated patients (57.3 %). In a 26-week long-term placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another 26-week long-term controlled trial, the incidence of EPS was 14.8% for patients treated with aripiprazole and 15.1% for patients treated with olanzapine.

Manic episodes in bipolar I disorder: In a 12-week controlled trial, the incidence of EPS was 23.5% for patients treated with aripiprazole and 53.3% for patients treated with haloperidol. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for patients treated with lithium. In the maintenance phase of a 26-week long-term placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

Akathisia
In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In patients with schizophrenia, the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

Dystonia
Class effect: in susceptible individuals, symptoms of dystonia, prolonged abnormal muscle group contractions may occur during the first days of treatment. Dystonic symptoms include: neck muscle spasm, sometimes progressing to throat tightness, difficulty swallowing, difficulty breathing, and/or protrusion of the tongue. Although these symptoms can occur with low doses, they are more common and more severe with high doses of the more potent first-generation antipsychotics. A high risk of acute dystonia is observed in males and in younger age groups.

Prolactin
In clinical trials for approved indications and post-marketing, both increases and decreases in serum prolactin from baseline were observed with aripiprazole (section 5.1).

Laboratory parameters
Comparisons between aripiprazole and placebo for the percentages of patients with potentially clinically relevant changes in routine laboratory test parameters and lipid parameters (see section 5.1) revealed no clinically important differences. Elevations of creatine phosphokinase (CPK), usually transient and asymptomatic, were observed in 3.5% of patients treated with aripiprazole compared with 2.0% of patients treated with placebo.

Pediatric population
Schizophrenia in adolescents aged 15 years and older
In a short-term, placebo-controlled clinical trial involving 302 adolescents (13-17 years of age) with schizophrenia, the frequency and type of adverse reactions were similar to those seen in adults, except for the following reactions which were reported more frequently in adolescents receiving aripiprazole than adults receiving aripiprazole (and more often than placebo):
Drowsiness/sedation and extrapyramidal disorder were reported very commonly (≥ 1/10), and dry mouth, increased appetite and orthostatic hypotension were reported frequently (≥ 1/100, < 1/10). The safety profile in the 26-week open-label extension trial was similar to that seen in the short-term, placebo-controlled trial.
The safety profile in a long-term, double-blind, placebo-controlled clinical trial was also similar except for the following reactions, which were reported more frequently than in pediatric patients taking placebo: decreased weight, increased insulin, arrhythmia and leukopenia were reported frequently (≥ 1/100, < 1/10).
In the population group of adolescents with schizophrenia (13-17 years of age) with exposure for up to 2 years, the incidence of low serum prolactin levels in females (< 3 ng/ml) and in males (< 2 ng/ml) was 29.5% and 48.3%, respectively. In the population group of adolescents with schizophrenia (13-17 years of age) with aripiprazole exposure of 5 to 30 mg for up to 72 months, the incidence of low serum prolactin levels in females (< 3 ng/ml) and in males (< 2 ng/ml) was 25.6 % and 45.0 %, respectively.
In two long-term trials of adolescent (13-17 years of age) schizophrenic and bipolar patients treated with aripiprazole, the incidence of low serum prolactin levels in females (< 3 ng/ml) and males (< 2 ng/ml) was 37.0% and 59.4%, respectively.

Manic episodes in bipolar I disorder in adolescents 13 years of age and older
The frequency and type of adverse reactions in adolescents with bipolar I disorder were similar to those seen in adults, with the exception of the following reactions: very common (≥ 1/10) somnolence (23.0%), extrapyramidal disorder (18.4%), akathisia (16.0%), and fatigue (11.8%); and common (≥ 1/100, < 1/10) high abdominal pain, increased heart rate, weight gain, increased appetite, muscle spasms and dyskinesia.
The following adverse reactions had a possible dose-response relationship: extrapyramidal disorder (incidences were 10 mg, 9.1%, 30 mg, 28.8%, placebo, 1.7%); and akathisia (incidences were 10 mg, 12.1%, 30 mg, 20.3%, placebo, 1.7%).

At weeks 12 and 30, the mean changes in body weight of adolescents with bipolar I disorder for aripiprazole were 2.4 kg and 5.8 kg and for placebo were 0.2 kg and 2.3 kg, respectively.
In the pediatric population, somnolence and fatigue were more frequently observed in patients with bipolar disorder compared to patients with schizophrenia.
In the pediatric bipolar population (10-17 years) with exposure up to 30 weeks, the incidence of low serum prolactin levels in females (< 3 ng/ml) and males (< 2 ng/ml) was of 28.0% and 53.3%, respectively.

Pathological gambling and other impulse control disorders
In patients treated with aripiprazole, pathological gambling, hypersexuality, compulsive shopping or binge eating may occur (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signals and symptons
In clinical trials and post-marketing experience, accidental or intentional acute overdose with aripiprazole alone has been identified in adult patients with estimated doses reported up to 1260 mg, with no fatalities. Potentially medically important signs and symptoms included lethargy, increased blood pressure, drowsiness, tachycardia, nausea, vomiting, and diarrhea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received, with no fatalities. Reported signs and symptoms, potentially medically serious, included somnolence, transient loss of consciousness, and extrapyramidal symptoms.

Overdose control
Overdose management should focus on supportive therapy with adequate airway maintenance, oxygenation and ventilation, and symptom control. The possibility of multiple drug involvement should be considered. Consequently, cardiac monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. After any confirmation or suspicion of overdose with aripiprazole, medical surveillance and careful monitoring should be maintained until the patient recovers.
Activated charcoal (50 g), given one hour after aripiprazole, decreased aripiprazole Cmax by about 41% and AUC by about 51%, suggesting that charcoal may be effective in treating overdose.

Hemodialysis
Although there is no information on the effect of hemodialysis in the treatment of overdose with aripiprazole, hemodialysis is unlikely to be useful in the management of overdose, as aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antipsychotics, ATC code: N05AX12

Mechanism of action

The efficacy of aripiprazole in schizophrenia and bipolar I disorder has been proposed to be mediated through a combination of partial agonism at dopamine D2 and serotonergic 5-HT1A receptors and antagonism at serotonergic 5-HT2A receptors. Aripiprazole exhibited antagonistic properties in animal models of dopaminergic hyperactivity and agonistic properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited in vitro high binding affinity for dopamine D2 and D3 and serotonergic 5-HT1A and 5-HT2A receptors and moderate affinity for dopaminergic D4, serotonergic 5-HT2C and 5-HT7, alpha 1 adrenergic and H1 histamine receptors. Aripiprazole also exhibited moderate binding affinity for serotonin reuptake sites and no appreciable affinity for muscarinic receptors. Interaction with receptors other than the dopaminergic and serotonergic subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole doses of 0.5 to 30 mg administered once daily to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-racloprid, a specific D2/D3 receptor ligand to CT-detected caudates and putamen of positron emission.

Clinical efficacy and safety

Adults

Schizophrenia

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 adult schizophrenic patients, with both negative and positive symptoms, aripiprazole was statistically associated with significantly greater improvements in psychotic symptoms compared to placebo.

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

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

Weight gain

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, multinational, double-blind, olanzapine-controlled study of schizophrenia in which 314 adult patients were enrolled and the primary endpoint was weight gain, significantly fewer patients receiving aripiprazole (n = 18, or 13% of evaluable patients) had at least 7% weight gain from baseline (i.e., an increase of at least 5.6 kg for a mean baseline weight of around 80.5 kg) compared to with olanzapine (n = 45, or 33% of evaluable patients).

Lipid parameters

In a group analysis of lipid parameters from placebo-controlled clinical trials in adults, aripiprazole was not shown to induce clinically relevant changes in total cholesterol, triglycerides, HDL and LDL levels.

Prolactin
Prolactin levels were assessed in all trials of all doses of aripiprazole (n = 28,242). The incidence of hyperprolactinemia or increased serum prolactin in patients treated with aripiprazole (0.3%) was similar to that observed with placebo (0.2%). For patients receiving aripiprazole, the median time to onset was 42 days and the median duration was 34 days.
The incidence of hypoprolactinemia or decreased serum prolactin in patients treated with aripiprazole was 0.4% compared to 0.02% for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and the median duration was 194 days.

Manic episodes in bipolar I disorder
In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic episode or mixed episode of bipolar I disorder, aripiprazole demonstrated superior efficacy to placebo in reducing manic symptoms for 3 weeks. These trials included patients with or without psychotic episodes and with or without rapid cyclic courses.
In a 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic episode or mixed episode of bipolar I disorder, aripiprazole failed to demonstrate superior efficacy to placebo.
In two 12-week, placebo-controlled, active-comparator monotherapy trials in patients with a manic episode or mixed episode of bipolar I disorder, with or without psychotic episodes, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at 12 weeks. Aripiprazole at week 12 also demonstrated a comparable proportion of patients in symptomatic remission of mania compared to lithium or haloperidol.
In a 6-week, placebo-controlled trial involving patients with a manic episode or mixed episode of bipolar I disorder, with or without psychotic episodes, who were partially unresponsive to lithium or valproate alone for 2 weeks at therapeutic serum concentrations, addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reducing manic symptoms compared to lithium or haloperidol monotherapy.
In a 26-week, placebo-controlled trial followed by a 74-week extension in manic patients who achieved remission during aripiprazole treatment in a stabilization phase prior to randomisation, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence for mania, but failed to demonstrate superiority over placebo in preventing recurrence for depression.
In a 52-week, placebo-controlled trial in patients with an ongoing manic or mixed episode of bipolar I disorder who achieved sustained remission (Y-MRS and MADRRS total scores ≤ 12) with aripiprazole (10 mg/day at 30 mg/day) as add-on therapy to lithium or valproate for 12 consecutive weeks, add-on therapy with aripiprazole demonstrated superiority over placebo with a 46% risk decrease (hazard ratio 0.54) in preventing bipolar recurrence and a 65% risk decrease (hazard ratio 0.35) in preventing recurrence for mania over adjuvant placebo therapy, but failed to demonstrate superiority over placebo in preventing recurrence for depression. Adjuvant therapy with aripiprazole demonstrated superiority over placebo in the secondary outcome measure, CGI-BP, Severity of Disease (mania) score. In this trial, to determine partial lack of response, patients were assigned by investigators to open-label lithium or valproate monotherapy. Patients were stabilized for at least 12 consecutive weeks with aripiprazole in combination with the same mood stabilizer. The stabilized patients were then randomized to continue double-blind therapy with the same mood stabilizer in combination with aripiprazole or placebo. In

the randomization phase, four subgroups of mood stabilizers were evaluated: aripiprazole + lithium, aripiprazole + valproate, placebo + lithium and placebo + valproate. For the adjuvant treatment arm, Kaplan-Meier rates obtained for recurrence to any mood episode were 16% for aripiprazole + lithium and 18% for aripiprazole + valproate compared with 45% for placebo + lithium and 19% for placebo + valproate.

Paediatric population

Schizophrenia in teenagers
In a 6-week placebo-controlled trial involving 302 adolescent patients with schizophrenia (13-17 years of age) with positive or negative symptoms, aripiprazole was associated with statistically greater and significant improvements in psychotic symptoms compared to placebo. In a subanalysis of adolescent patients aged 15 to 17 years, representing 74% of the total participating population, maintenance of the effect was observed during the 26-week open-label extension trial.
In a 60 to 89 week, double-blind, randomized, placebo-controlled trial involving adolescents (n = 146; 13-17 years of age) with schizophrenia, a statistically significant difference in the rate of relapse of psychotic symptoms was observed between the aripiprazole (19.39%) and placebo (37.50%) treatment groups. The point estimate of the hazard ratio was 0.461 (95% confidence interval: 0.242-0.879) for the entire population. In subgroup analyses, the point estimate of the hazard ratio in subjects aged 13 to 14 years was 0.495, compared with 0.454 among subjects aged 15 to 17 years. However, the estimate of the hazard ratio for the younger group (13-14 years) was not accurate, reflecting the small number of subjects in this group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this estimate (range 0.151 to 1.628) did not allow conclusions to be drawn about the presence of a treatment effect. In contrast, the 95% confidence interval for the hazard ratio of the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879, so a treatment effect can be concluded in older patients.

Manic episodes in bipolar I disorder in children and adolescents
Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10-17 years of age) who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for bipolar I disorder with manic or with or without psychotic symptoms and who scored ≥ 20 on the Young Mania Rating Scale (Y-MRS) at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current comorbid diagnosis for ADHD (Attention Deficit Hyperactivity Disorder).
At weeks 4 and 12, aripiprazole was superior to placebo in the change from baseline in the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in patients with ADHD-associated comorbidity compared with the non-ADHD that did not differ from placebo. Relapse prevention has not been established.

In patients receiving 30 mg, the most frequent adverse events requiring urgent treatment are extrapyramidal disorder (28.3%), somnolence (27.3%), headache (23.2%) and nausea (14.1%). The mean weight gain was 2.9 kg over the 30-week treatment interval, compared to placebo-treated patients who gained 0.98 kg.

Irritability associated with autistic disorder in pediatric patients (see section 4.2)
Aripiprazole has been studied in patients aged 6 to 17 years in two eight-week placebo-controlled trials [a flexible dose (2-15 mg/day) and a fixed dose (5, 10 or 15

mg/day)] and in a 52-week open-label trial. The dose initially administered in these trials was 2 mg/day, increasing to 5 mg/day after one week, with subsequent weekly increases of 5 mg/day to the target dose. More than 75% of patients were under 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behavior Checklist Irritability subscale. However, the clinical relevance of these results has not yet been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In pooled trials, the incidence of low serum prolactin levels in females (< 3 ng/ml) and male subjects (< 2 ng/ml) in aripiprazole-treated patients was 27/46 (58,7%) and 258/298 (86.6%), respectively. In placebo-controlled clinical trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.
Aripiprazole was also studied in a long-term, placebo-controlled maintenance trial. Patients with a stable response after 13-26 weeks of stabilization with aripiprazole (2-15 mg/day) either continued treatment with aripiprazole or switched to placebo for an additional 16 weeks. Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo; the 16-week relapse hazard ratio (aripiprazole/placebo) was 0.57 (non-statistically significant). In the second phase (16 weeks) of the trial, an average weight gain during the stabilization phase (up to 26 weeks) with aripiprazole of 3.2 kg and an additional average gain of 2.2 kg for aripiprazole compared to 0 was observed 6 kg for the placebo. Extrapyramidal symptoms were mainly reported during the stabilization phase in 17% of patients, with tremor accounting for 6.5%.

Tics associated with Tourette Syndrome in pediatric patients (see section 4.2)
The efficacy of aripiprazole was studied in pediatric patients with Tourette Syndrome (aripiprazole: n = 99, placebo: n = 44) in an 8-week, randomized, double-blind, placebo-controlled study using a treatment-based group model in weight, with a fixed dose in the dose range of 5 mg/day to 20 mg/day and an initial dose of 2 mg. Patients were between 7 and 17 years of age and had a mean baseline value of 30 on the Yale Global Tic Severity Scale (YGTSS) total tic score (TTS). Aripiprazole showed an improvement in TTS-YGTSS change from baseline to week 8 of 13.35 for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg), compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in pediatric patients with Tourette's Syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated with a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10-week, randomized, double-blind, placebo-controlled study conducted in South Korea. Patients were aged between 6 and 18 years, and had a mean baseline TTS-YGTSS score of 29. The aripiprazole group had an improvement in TTS-YGTSS change from baseline to week 10 of 14.97 compared to an improvement of 9.62 in the placebo group.
In both short-term studies, the clinical relevance of the efficacy results was not established, considering the magnitude of the treatment effect compared to the large placebo effect and the unclear effects on psychosocial functioning. Long-term data regarding the efficacy and safety of aripiprazole in this fluctuating disease are not available.
The European Medicines Agency has deferred the obligation to submit the results of studies with aripiprazole in one or more subsets of the pediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for more information on pediatric use).

5.2 Pharmacokinetic properties

Absorption
Aripiprazole is well absorbed, and peak plasma concentrations occur between 3-5 hours after administration. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. A high-fat meal does not affect 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, the binding of aripiprazole and dehydro-aripiprazole to serum proteins is greater than 99%, mainly binding to albumin.

Biotransformation
Aripiprazole is extensively metabolized by the liver, mainly through three biotransformation pathways: dehydrogenation, hydroxylation and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for the dehydrogenation and hydroxylation of aripiprazole and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug fraction in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, accounts for about 40% of the plasma AUC of aripiprazole.

Elimination
The mean elimination half-lives for aripiprazole are approximately 75 hours in CYP2D6 extensive metabolizers and approximately 146 hours in CYP2D6 poor metabolizers.
The total body clearance of aripiprazole is 0.7 ml/min/kg and is mainly hepatic.
After a single oral dose of 14C-labeled 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.

Paediatric population
The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients aged 10 to 17 years were similar to those in adults after correction for body weight differences.

Pharmacokinetics in special patient groups
Seniors
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable age-dependent effect in a population pharmacokinetic analysis in schizophrenic patients.

Sex
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects, nor is there any detectable sex-dependent effect in a population pharmacokinetic analysis in schizophrenic patients.

Smoking habits
Assessment of population pharmacokinetics revealed no evidence of clinically significant smoking-related differences in the pharmacokinetics of aripiprazole.

Breed

The population pharmacokinetic evaluation did not reveal any evidence of race-related differences in the pharmacokinetics of aripiprazole.

Renal impairment
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were similar in patients with severe kidney disease compared to healthy young subjects.

Hepatic impairment
A single-dose study in subjects with liver cirrhosis of varying grade (Child-Pugh Class 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 conclude about its metabolic capacity.

5.3 Preclinical safety data
Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.
Significant toxicological effects were only observed from exposure levels considered sufficiently in excess of the maximum human exposure level, indicating that these effects were limited or not relevant for 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 10 times the mean steady-state AUC at the human dose recommended maximum) and increase in adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in the female rat at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest non-tumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.
An additional result was cholelithiasis as a consequence of precipitation of sulfate conjugates of hydroxylated metabolites of aripiprazole in the bile of monkeys after repeated oral administration at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the clinical dose) recommended maximum dose or 16 to 81 times the maximum recommended human dose on a mg/m2 basis). However, the concentrations of hydroxylated aripiprazole sulfate conjugates in human bile at the highest proposed dose, 30 mg daily, were no greater than 6% of the bile concentrations found in monkeys in the 39-week study and are well below (6%) their in vitro solubility limits.
In repeated dose studies in rats and young dogs, the toxicity profile of aripiprazole was comparable to that seen in adult animals, and there was no evidence of neurotoxicity or adverse developmental effects.
Based on the results of all standard genotoxicity tests, aripiprazole was found to be non-genotoxic. Aripiprazole did not alter fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed fetal ossification and possible teratogenic effects, was 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 steady-state AUC average at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those causing developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipientes

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Anhydrous colloidal silica
Magnesium stearate
Vanilla scent
Aspartame
Red iron oxide (E 172) - for the 10 mg and 30 mg strengths
Yellow iron oxide (E 172) - for the 15 mg strength

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
The medicine does not require any special storage precautions.

6.5 Nature and contents of container
Aluminium-aluminium blisters, in packs of 14, 28 and 49 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medication or waste must be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
Pygen Ltd.
Av. do Lago, no. 470-470ª-470B, Atelier 6
2765-420
Estoril

8. MARKETING AUTHORIZATION NUMBER(S)

Zalonil 10 mg orodispersible tablets
14 orodispersible tablets – Registration No. 5751623 at INFARMED I.P.
28 orodispersible tablets – Registration No. 5751631 at INFARMED I.P.
49 orodispersible tablets – Registration No. 5751649 at INFARMED I.P.

Zalonil 15 mg orodispersible tablets
14 orodispersible tablets – Registration No. 5751748 at INFARMED I.P.
28 orodispersible tablets – Registration No. 5751755 at INFARMED I.P.
49 orodispersible tablets – Registration No. 5751763 at INFARMED I.P.

Zalonil 30 mg orodispersible tablets
14 orodispersible tablets – Registration No. 5751805 at INFARMED I.P.
28 orodispersible tablets – Registration No. 5751813 at INFARMED I.P.

49 orodispersible tablets – Registration No. 5751821 at INFARMED I.P.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF MARKETING AUTHORISATION

Date of first authoriszation: 06/04/2018

10. DATE OF REVISION OF THE TEXT

30 October 2020