**SCHEDULING STATUS**
S5

**PROPRIETARY NAMES AND DOSAGE FORM**
**APRIPENT™ 5** tablets
**APRIPENT™ 10** tablets
**APRIPENT™ 15** tablets
**APRIPENT™ 30** tablets

**COMPOSITION**

**Active ingredient:**
**APRIPENT 5** tablets contain 5 mg of aripiprazole
**APRIPENT 10** tablets contain 10 mg of aripiprazole
**APRIPENT 15** tablets contain 15 mg of aripiprazole
**APRIPENT 30** tablets contain 30 mg of aripiprazole

**Inactive ingredients:**
Croscarmellose sodium, crystalline maltose, magnesium stearate, microcrystalline cellulose, pregelatinised starch. The colourants are: indigo carmine (5 mg tablet), iron oxide red (10 mg and 30 mg tablets), iron oxide yellow (15 mg tablet). Contains sugar: (crystalline maltose).

| | Maltose content: |
|---|---|
| 5 mg tablet: | 28 mg/tablet |
| 10 mg tablet: | 56 mg/tablet |
| 15 mg tablet: | 84 mg/tablet |
| 30 mg tablet: | 168 mg/tablet |

**CATEGORY AND CLASS**
A 2.6.5 Tranquillisers - miscellaneous structures

**PHARMACOLOGICAL ACTION**

**Pharmacodynamic properties**
a Aripiprazole is a quinolinone derivative and is an atypical antipsychotic.
It is thought that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine $D_2$ and serotonin $5HT_{1a}$ receptors and antagonism of serotonin $5HT_{2a}$ receptors.
Aripiprazole has high binding affinity *in vitro* for dopamine $D_2$ and $D_3$, serotonin $5HT_{1a}$ and $5HT_{2a}$ receptors and moderate affinity for dopamine $D_4$, serotonin $5HT_{2c}$ and $5HT_7$, $alpha_1$ adrenergic and histamine $H_1$ receptors. Aripiprazole also has 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.

**Pharmacokinetic properties**
**APRIPENT** activity is primarily due to the parent compound, aripiprazole.

***Absorption:***
Aripiprazole is well absorbed after oral administration of **APRIPENT**, with peak plasma concentrations occurring within 3 to 5 hours after dosing.
The absolute oral bioavailability of **APRIPENT** is 87 %.
The bioavailability of aripiprazole is not significantly affected by administration with food.
Steady-state concentrations are reached within 14 days of dosing. At steady-state, the pharmacokinetics of aripiprazole is dose-proportional.

***Distribution:***
Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 l/ kg. At therapeutic concentrations, aripiprazole is more than 99 % bound to serum proteins, primarily albumin.
With multiple dosing, aripiprazole accumulates by a factor of 5.

***Metabolism:***
Aripiprazole undergoes minimal pre-systemic metabolism; it is extensively metabolised by the liver, primarily via three biotransformation pathways: dehydrogenation, hydroxylation and N-dealkylation.
CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, with N-dealkylation being catalysed by CYP3A4.
Aripiprazole is the predominant active moiety in the systemic circulation.
The predominant metabolite in human plasma is dehydro-aripiprazole, with about the same affinity for the $D_2$ receptors as the parent compound.
At steady-state dehydro-aripiprazole, the active metabolite, represents about 39 % of aripiprazole AUC in plasma.

***Elimination:***
The total body clearance of aripiprazole is 0,7 ml/min per kg, which is primarily mediated by the hepatic system.
Less than 1 % unchanged aripiprazole is excreted in the urine and approximately 18 % of the oral dose is recovered unchanged in the faeces.
The mean elimination half-life of aripiprazole is about 75 hours.

***Special populations:***

*Hepatic impairment*
In patients with liver cirrhosis (Child-Pugh Classes A, B and C), the AUC of aripiprazole increases about 31 % with mild hepatic impairment and 8 % with moderate hepatic impairment; it decreases about 20 % with severe hepatic impairment. These differences do not require dose adjustment.

*Renal impairment*
In patients with severe renal impairment (creatinine clearance < 30 ml/min), the $C_{max}$ of aripiprazole and dehydro-aripiprazole increases, but the AUC is about 15 % lower for aripiprazole and 7 % higher for dehydro-aripiprazole.
No dosage adjustment is required in subjects with renal impairment.

*Elderly*
Aripiprazole clearance is about 20 % lower in elderly (65 years or older) patients, compared to younger patients.
No dosage adjustments are recommended for elderly patients (however, see **WARNINGS AND SPECIAL PRECAUTIONS**, ***Increased mortality in elderly patients with dementia-related psychosis***).

*Gender*
$C_{max}$ and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40 % higher in women than in men; the apparent clearance of aripiprazole is lower in women after oral administration. These differences, however, are largely explained by differences in body mass (about 25 %) between men and women. No dosage adjustment is recommended based on gender.

B

## INDICATIONS

**APRIPENT** is indicated for:
- the treatment of schizophrenia and for the maintenance of clinical improvement in adults;
- the treatment of acute manic episodes in bipolar I disorder and
- for the prevention of recurrence of new manic episodes in patients who experienced predominantly manic episodes and who responded to **APRIPENT** treatment.

## CONTRAINDICATIONS

**APRIPENT** is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients of **APRIPENT**.
**APRIPENT** is not indicated for use in elderly patients with dementia-related psychosis; see **WARNINGS AND SPECIAL PRECAUTIONS**.
**Paediatric use:** The safety and efficacy of **APRIPENT** in children and adolescents under 18 years of age have not been established. The use of **APRIPENT** is therefore not indicated for this population.

## WARNINGS AND SPECIAL PRECAUTIONS

**Increased mortality in elderly patients with dementia-related psychosis**

**APRIPENT is not approved for the treatment of patients with dementia-related psychosis (see CONTRAINDICATIONS). Elderly patients with dementia-related psychosis treated with APRIPENT, are at increased risk of death compared to placebo**

Most of the deaths reported in elderly patients with dementia-related psychosis appeared to be either due to cardiovascular causes (e.g. heart failure, sudden death) or infections (e.g. pneumonia). See **Cerebrovascular adverse events (CVAE)** below.

**Suicidality**
There is an increased risk of suicide attempts in patients with psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with **APRIPENT** (see **SIDE EFFECTS**). High-risk patients (clinical worsening of depression, suicidal ideation and unusual changes in behaviour) should be closely observed when **APRIPENT** is prescribed. The risk of suicide persists beyond the first four weeks of treatment for atypical antipsychotics including **APRIPENT**.
To reduce the risk of overdose, prescriptions for **APRIPENT** should be written for the smallest quantity of tablets consistent with good patient management.

**Extrapyramidal symptoms**
Extrapyramidal dysfunction and resultant disorders may occur. These disorders include acute dystonia, a parkinsonism-like syndrome and akathisia; late effects include tardive dyskinesia and perioral tremor. See **SIDE EFFECTS**.

**Tardive dyskinesia**
The risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment, such as **APRIPENT**. If signs and symptoms of tardive dyskinesia appear in a patient it should be considered to reduce the dose of, or to discontinue, **APRIPENT**. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.
Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal side effects of antipsychotic medicines (such as **APRIPENT**), and the reaction can be extremely serious, even fatal. **APRIPENT** is however contraindicated in this population (see **CONTRAINDICATIONS**).

**Pathological gambling**
Pathological gambling has been reported. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully.

**Neuroleptic malignant syndrome**
A potentially fatal symptom complex, neuroleptic malignant syndrome (NMS), has been reported. NMS may manifest as hyperpyrexia, muscle rigidity, altered mental status and 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 medicines, including **APRIPENT**, must be discontinued.

**Seizures/ convulsions**
Seizures may occur with **APRIPENT** (the frequency is unknown). It should therefore be used with care in those with a history of seizures or with conditions that lower the seizure threshold (see **SIDE EFFECTS**, ***Nervous system disorders***).

**Cerebrovascular adverse events (CVAE), including stroke**
Cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, have also been reported in elderly patients with psychosis associated with Alzheimer's disease. **APRIPENT** is contraindicated in patients with dementia-related behavioural disturbances (see **CONTRAINDICATIONS** and boxed warning above). A significant dose response relationship for cerebrovascular

adverse reactions in patients treated with aripiprazole (such as **APRIPENT**) has been established.
- Before prescribing to elderly patients, medical practitioners should take into account risk predictions for stroke in the individual patient (e.g. hypertension, diabetes, current smoking, atrial fibrillation, and age > 80 years).
- Where the use of antipsychotics in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances (see **Falls and fractures** below), oversedation and complications associated with hyperglycaemia.

**Cardiovascular disorders**
Cases of venous thromboembolism (VTE) have been reported.
**APRIPENT** should be used with caution in patients with cardiovascular or cerebrovascular disease, or in those with conditions that would predispose to hypotension (dehydration, hypovolaemia and treatment with antihypertensive medicines) (see **SIDE EFFECTS**).

***Conduction abnormalities***
Tachycardia and orthostatic hypotension may occur less frequently with **APRIPENT** treatment; bradycardia, ventricular dysrhythmias, cardiac arrest, and sudden unexplained death have been reported at unknown frequency, as have QT prolongation and *torsade de pointes* (see **SIDE EFFECTS**).

***Orthostatic hypotension***
**APRIPENT** may cause orthostatic hypotension, which may be attributed to its $\alpha_1$-adrenergic receptor antagonism (see **SIDE EFFECTS**, ***Vascular disorders***).

**Falls and fractures (elderly patients (> 65 years)**
The risk of falls and hip fracture has been reported to be increased in elderly patients given antipsychotics. Where the use of antipsychotics such as **APRIPENT** in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances and oversedation.

**Metabolic changes**
**APRIPENT** alters endocrine and metabolic functions. Patients have developed amenorrhoea, galactorrhoea, hyperprolactinaemia and gynaecomastia, weight gain, hyperglycaemia and altered glucose tolerance. Body temperature regulation may be impaired and may result in hypo- or hyperthermia depending on environment. There have also been reports of hypercholesterolaemia.

***Hyperglycaemia and diabetes mellitus***
Hyperglycaemia may in some cases be extreme and associated with ketoacidosis or hyperosmolar coma or death (see **SIDE EFFECTS**, ***Metabolism and nutrition disorders***).
Patients with diabetes mellitus or with risk factors for diabetes mellitus (with a family history of diabetes or who are obese), should be monitored regularly for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness.
Patients who develop symptoms of hyperglycaemia during treatment with **APRIPENT** should undergo fasting blood glucose testing. Hyperglycaemia may be resolved when **APRIPENT** is discontinued; however, some patients may still need continuation of anti-diabetic treatment.

***Dyslipidaemia***
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, such as **APRIPENT**.

***Weight gain***
Weight gain has been reported; usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. If weight gain is clinically significant, dose reduction should be considered.

**Blood dyscrasias**
Blood dyscrasias, including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia may occur (see **SIDE EFFECTS**, ***Blood and the lymphatic system disorders***).
Patients with a history of clinically significant low white blood cell count (WBC) or medicine-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy. Discontinuation of **APRIPENT** should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

**Potential for cognitive and motor impairment**
Antipsychotics, including **APRIPENT**, may have the potential to impair judgment, thinking, or motor skills (see **SIDE EFFECTS** and **Effects on ability to drive and use of machines**).

**Body temperature regulation**
Antipsychotic medicines, such as **APRIPENT**, may disrupt the body's ability to reduce the core body temperature. Appropriate care is advised when prescribing **APRIPENT** for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving a concomitant medicine with anticholinergic activity, or being subject to dehydration.

**Dysphagia**
**APRIPENT** may possibly cause oesophageal dysmotility and aspiration; it should be used with caution in patients at risk of pneumonia.

**Patients with ADHD comorbidity**
Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of **APRIPENT** and stimulants; therefore, extreme caution should be taken when these medicines are co-administered.

**Maintenance therapy**
During antipsychotic treatment, including **APRIPENT**, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.
Patients should be periodically reassessed to determine the usefulness of continuation of maintenance treatment; the effectiveness of long-term use (more than 6 months) has not been documented.

**Other medicines**
Simultaneous administration of **APRIPENT** and parenteral benzodiazepine may be associated with excessive sedation and cardiorespiratory depression (see **INTERACTIONS**). If supplementation with parenteral benzodiazepine therapy is deemed necessary,

patients should be monitored for excessive sedation and for orthostatic hypotension.

**Effects on ability to drive and use of machines**
**APRIPENT** may cause somnolence, fatigue, blurred vision, dizziness and lightheadedness and may potentially impair judgment, thinking or motor skills.
Patients should therefore not operate hazardous machinery, including motor vehicles before they are reasonably certain that **APRIPENT** does not adversely affect them.

**Information on excipients**
**APRIPENT** contains maltose, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase/ isomaltase insufficiency should not take **APRIPENT**.

## INTERACTIONS

**Potential effect of other medicines on APRIPENT**

***CYP2D6 inhibitors (quinidine, fluoxetine, paroxetine etc.):***
The AUC of aripiprazole is significantly increased by CYP2D6 inhibitors, but the $C_{max}$ is not affected. **APRIPENT** dose should be reduced to about one-half of its prescribed dose when concomitant administration with these medicines occurs.

***CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, HIV protease inhibitors):***
Concomitant use of CYP3A4 inhibitors causes significant increases in aripiprazole and dehydro-aripiprazole's AUC and $C_{max}$.
In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole (contained in **APRIPENT**) compared to that in CYP2D6 extensive metabolisers.
When considering concomitant use of potent CYP3A4 inhibitors with **APRIPENT**, potential benefits should exceed the potential risks to the patient. If used at all, **APRIPENT** dose should be reduced to approximately one-half of its prescribed dose.
If the CYP2D6 or the CYP3A4 inhibitor is discontinued, the dosage of **APRIPENT** should be increased to the level prior to the initiation of the concomitant therapy.

***CYP3A4 inducers (e.g. carbamazepine, rifampicin, rifabutin, phenytoin, phenobarbital (phenobarbitone), primidone, efavirenz, nevirapine and St. John's Wort):***
Concomitant use of CYP3A4 inducers causes significant decreases in aripiprazole and dehydro-aripiprazole's AUC and $C_{max}$.
**APRIPENT** dose should be doubled when prescribed concomitantly with potent CYP3A4 inducers.
The use of CYP3A4 inducers for longer than 14 days should be avoided.
Upon discontinuation of potent CYP3A4 inducers, the dosage of **APRIPENT** should be reduced to the recommended dose.

***Other serotonergic medicines:***
Cases of serotonin syndrome have been reported in patients taking aripiprazole (contained in **APRIPENT**). Possible signs and symptoms for this condition can occur, especially in cases of concomitant use with other serotonergic medicines, such as SSRI/SNRI, or with medicines that are known to increase aripiprazole concentrations such as diltiazem (see **SIDE EFFECTS**).
***Famotidine***, an $H_2$-antagonist, reduces the rate of absorption of aripiprazole, but has no clinically significant effect on its pharmacokinetics.

**Potential effect of APRIPENT on other medicines**
Due to its $\alpha_1$-adrenergic receptor antagonist activity, **APRIPENT** may enhance the effect of certain antihypertensive medicines.
See **WARNINGS AND SPECIAL PRECAUTIONS**, ***Orthostatic hypotension***.
Caution should be used if **APRIPENT** is prescribed concomitantly with medicines that prolong the QT interval or cause electrolyte imbalance (see **WARNINGS AND SPECIAL PRECAUTIONS** and **SIDE EFFECTS**).
**APRIPENT** should be used with caution in combination with other centrally acting substances, such as benzodiazepines.
It is not expected that **APRIPENT** would cause clinically important effects on medicines metabolised by substrates of CYP2D6, CYP2C9, CYP2V19 and CYP3A4.

**Effect of food and drink**
Use of alcohol with **APRIPENT** should be avoided.

## HUMAN REPRODUCTION
Safety of use of **APRIPENT** during pregnancy and lactation has not been established.
Congenital anomalies have been reported. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during treatment with **APRIPENT**.
Neonates exposed to antipsychotics (including **APRIPENT**) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Aripiprazole is excreted in human breast milk. **APRIPENT** should not be prescribed during pregnancy and lactation.

C

## DOSAGE AND DIRECTIONS FOR USE

**Schizophrenia**
The recommended starting dose for **APRIPENT** is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.
**APRIPENT** is effective in a dose range of 10 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.

**Bipolar mania**
The recommended starting dose for **APRIPENT** is 15 mg, administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see **INTERACTIONS**). 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:***
For preventing recurrence of manic episodes in patients who have been receiving **APRIPENT**, continue therapy at the same dose. Adjustments of daily dose, including dose reduction should be considered on the basis of clinical status.
Prevention of depressive episodes using **APRIPENT** monotherapy has not been established. Supplementary therapy should be

considered for the prevention or treatment of depressive episodes, as clinically appropriate.

**Concomitant medicines:**

***Dosage adjustment for patients taking APRIPENT concomitantly with potent CYP3A4 or CYP2D6 inhibitors:***

- When a potent CYP3A4 or CYP2D6 inhibitor is given concomitantly with **APRIPENT**, the **APRIPENT** dose should be reduced to one-half of the usual dose.
- When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the **APRIPENT** dose should be increased.

***Dosage adjustment for patients taking potent CYP3A4 inducers:***

- When a potent CYP3A4 inducer is added to **APRIPENT** therapy, the **APRIPENT** dose should be doubled. Additional dose increases should be based on clinical evaluation.
- When the CYP3A4 inducer is withdrawn from the combination therapy, the **APRIPENT** dose should be reduced.

## SIDE EFFECTS

***Blood and the lymphatic system disorders***
*Frequency unknown:* agranulocytosis, leukopenia, neutropenia, thrombocytopenia

***Immune system disorders***
*Frequency unknown:* allergic reaction, anaphylactic reaction, angioedema

***Endocrine disorders***
*Less frequent:* hyperprolactinemia
*Frequency unknown:* diabetic ketoacidosis (DKA), diabetic hyperosmolar coma

***Metabolism and nutrition disorders***
*Frequent:* weight gain, diabetes mellitus
*Frequency unknown:* weight decreased, anorexia, hyponatraemia, hyperglycaemia

***Psychiatric disorders***
*Frequent:* insomnia, somnolence, sedation, restlessness, anxiety, agitation
*Less frequent:* depression*, hypersexuality
*Frequency unknown:* nervousness, pathological gambling, suicide attempt, suicidal ideation, suicide completed
(see **WARNINGS AND SPECIAL PRECAUTIONS**)

***Nervous system disorders***
*Frequent:* headache, dizziness, lightheadedness, akathisia, tremor, extrapyramidal disorder
*Less frequent:* Tardive dyskinesia, dystonia[1]
*Frequency unknown:* speech disorder, NMS, grand mal convulsion, serotonin syndrome, seizures, tardive dyskinesia

***Eye disorders***
*Frequent:* blurred vision
*Less frequent:* diplopia

***Cardiac disorders***
*Less frequent:* tachycardia*
*Frequency unknown:* QT prolongation, ventricular dysrhythmias, sudden unexplained death, cardiac arrest, *torsade de pointes*, bradycardia

***Vascular disorders***
Less frequent: orthostatic hypotension*
*Frequency unknown:* syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis), cerebrovascular accident (fatal)[2]

***Respiratory, thoracic and mediastinal disorders***
*Less frequent:* Hiccups
*Frequency unknown:* oropharyngeal spasm, laryngospasm, aspiration pneumonia, cough

***Gastrointestinal disorders***
*Frequent:* vomiting, nausea, dyspepsia, constipation, salivary hypersecretion
*Frequency unknown:* pancreatitis, dysphagia, dry mouth, abdominal discomfort, stomach discomfort, diarrhoea

***Hepatobiliary disorders***
*Frequency unknown:* jaundice, hepatitis, hepatic failure, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma glutamyl transferase (GGT), increased alkaline phosphatase

***Skin and subcutaneous tissue disorders***
*Frequency unknown:* rash, photosensitivity reaction, alopecia, hyperhidrosis

***Musculoskeletal, connective tissue and bone disorders***
*Frequency unknown:* rhabdomyolysis, myalgia, stiffness

***Renal and urinary disorders***
*Frequency unknown:* urinary incontinence, urinary retention

***Pregnancy, puerperium and perinatal conditions***
*Frequency unknown:* medicine withdrawal syndrome neonatal (see **PREGNANCY AND LACTATION**)

***Reproductive system and breast disorders***
*Frequency unknown:* priapism

***General disorders and administration site conditions***
*Frequent:* asthenia/fatigue
*Frequency unknown:* temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema

***Investigations***
*Frequency unknown:* increased creatine phosphokinase, increased blood glucose[3], blood glucose fluctuation, glycosylated haemoglobin increased

***Notes:***

* Possibly medically relevant side effects

**[1].** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic medicines. An elevated risk of acute dystonia has been observed in males and younger age groups.

**[2].** Cerebrovascular adverse reactions and increased mortality have been reported in elderly patients with dementia-related psychosis (see **WARNINGS AND SPECIAL PRECAUTIONS**).

**[3].** Hyperglycaemia and diabetes mellitus have been reported (see ***Endocrine disorders*** above and **WARNINGS AND SPECIAL PRECAUTIONS**).

## KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

**Symptoms of overdosage**
Symptoms of overdosage may include lethargy, increased blood pressure, somnolence, tachycardia and vomiting. The potentially medically serious signs and symptoms include somnolence, extrapyramidal symptoms and transient loss of consciousness.

**Treatment of overdosage**
Management of overdosage should include supportive therapy, maintenance of an adequate airway, oxygenation and ventilation and management of symptoms.
The possibility of multiple medicine involvement should be considered; cardiovascular monitoring should therefore commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias. Following any confirmed or suspected overdose of **APRIPENT**, close medical supervision and monitoring should continue until the patient recovers.
Activated charcoal (50 g), administered one hour after **APRIPENT**, may be effective for overdose management.
There is no information on the effect of haemodialysis in treating an overdose with **APRIPENT**, but haemodialysis is unlikely to be useful in overdose management as **APRIPENT** is not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

## IDENTIFICATION

**APRIPENT 5:**
Light blue to blue, mottled, round, biconvex tablets, engraved with “5” on one side and plain on the other side.

**APRIPENT 10:**
Pink, round, biconvex tablets, engraved with “10” on one side and plain on the other side.

**APRIPENT 15:**
Yellow, round, biconvex tablets, engraved with “15” on one side and plain on the other side.

**APRIPENT 30:**
Pink, oval, biconvex tablets, engraved with “30” on one side and plain on the other side.

## PRESENTATION

**APRIPENT 5**, **10**, **15** and **30** are packed in either of the following:
- A cardboard box containing 28, 30, 96 or 100 tablets, packed in silver PA/ALL/PVC-aluminium foil blisters (alu-alu blister).
- A white opaque high density polyethylene (HDPE) bottle with a child resistant polypropylene (PP) screw cap with a mounted desiccant, containing 28, 30, 96 or 100 tablets.

Not all packing systems or sizes may necessarily be marketed.

## STORAGE INSTRUCTIONS

Store at or below 25 °C. Keep the blisters in the carton until required for use and keep the HDPE bottle well-closed. Protect from moisture.
KEEP OUT OF REACH OF CHILDREN.

## REGISTRATION NUMBERS

**APRIPENT 5:** 51/2.6.5/0663
**APRIPENT 10:** 51/2.6.5/0664
**APRIPENT 15:** 51/2.6.5/0665
**APRIPENT 30:** 51/2.6.5/0666

## NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION

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## DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date of registration: 15 May 2019
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