PRODUCT MONOGRAPH

^{Pr}PIPORTIL® L_4

(pipotiazine palmitate injection)
25 mg/mL and 50 mg/mL

Antipsychotic Agent

sanofi-aventis Canada Inc.
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Laval, Quebec H7L 4A8

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NAME OF DRUG

^{Pr}PIPORTIL® L_4
(pipotiazine palmitate injection)

THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

ACTION

Piportil® L_4 (pipotiazine palmitate) is the palmitic ester of pipotiazine, a piperidine phenothiazine with antipsychotic properties and weak sedative activity. The esterification of pipotiazine is responsible for its prolonged duration of action. The onset of action appears usually within the first 2 to 3 days after injection and the effects of the drug on psychotic symptoms are significant within one week. Improvement in symptomatology lasts from 3 to 6 weeks, but adequate control may frequently be maintained with one injection every 4 weeks. However, in view of the variations in individual response, careful supervision is required throughout treatment.

Piportil L_4 has actions similar to those of other phenothiazines. Among the different phenothiazine derivatives, Piportil L_4 appears to be less sedating and to have a weak propensity for causing hypotension or potentiating the effects of CNS depressants and anesthetics. However, it produces a high incidence of extrapyramidal reactions.

INDICATIONS

Piportil L_4 (pipotiazine palmitate) is indicated in the maintenance treatment of chronic non-agitated schizophrenic patients.

CONTRAINDICATIONS

Piportil L_4 (pipotiazine palmitate) should not be administered in the presence of circulatory collapse, altered states of consciousness or comatose states, particularly when these are due to intoxication with central depressant drugs (alcohol, hypnotics, narcotics, etc.). It is contraindicated in severely depressed patients, in the presence of blood dyscrasias, liver disease, renal insufficiency, pheochromocytoma, or in patients with severe cardiovascular disorders or a history of hypersensitivity to phenothiazine derivatives.

Pipotiazine palmitate is not indicated for the management of psychoneurotic patients or geriatric patients with confusion and/or agitation.

As with other phenothiazines, pipotiazine is contraindicated in patients with suspected or established subcortical brain damage, with or without hypothalamic damage, since a hyperthermic reaction with temperatures above 40°C may occur, sometimes not until 14 to 16 hours after drug administration.

Phenothiazine compounds should not be used in patients receiving large doses of hypnotics, due to the possibility of potentiation.

The safety and efficacy of pipotiazine palmitate in children have not been established. Therefore, Piportil L_4 is not indicated for use in children.

WARNINGS

Elderly Patients with Dementia

Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in elderly patients with dementia showed a mean 1.6 fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Piportil L4 is not indicated for the treatment of patients with dementia (see PRECAUTIONS, Use in Elderly, Use in Geriatric Patients with Dementia).

Severe adverse reactions requiring immediate medical attention may occur and are difficult to predict. Therefore, Piportil L_4 (pipotiazine palmitate) should be administered under the supervision of physicians experienced in the use of psychotropic drugs and facilities should be readily available to cope with any emergency situation.

The use of this drug may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Potentiation of the effects of alcohol may also occur.

As with other neuroleptics, very rare cases of QT interval prolongation have been reported with Piportil L_4. Neuroleptic phenothiazines may potentiate QT interval prolongation, which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or

acquired (i.e., drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment (See also PRECAUTIONS and ADVERSE REACTIONS).

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Piportil L_4 should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. The lowest effective dose and the shortest duration of treatment should be used, and treatment should be discontinued at the earliest opportunity, or if a satisfactory response cannot be obtained. If the signs and symptoms of tardive dyskinesia appear during treatment, discontinuation of Piportil L_4 should be considered.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) may occur in patients receiving antipsychotic drugs. NMS is characterized by hyperthermia, muscle rigidity, altered consciousness, and signs of autonomic instability including irregular blood pressure, tachycardia, cardiac arrhythmias and diaphoresis. Additional signs may include elevated serum creatine kinase, myoglobinuria (rhabdomyolysis), acute renal failure and leukocytosis. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Rare cases of priapism have been reported with antipsychotic use, such as Piportil L_4. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment. The most likely mechanism of action of priapism is a relative decrease in sympathetic tone.

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore Piportil L_4 should be used with caution in patients with risk factors for thromboembolism (see also ADVERSE REACTIONS).

Pregnant Women:
Non-teratogenic effects:

Neonates exposed to antipsychotic drugs including Piportil L_4 during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, various degrees of respiratory disorders ranging from tachypnoea to respiratory distress and bradycardia. Although these events occurred most often when other drugs such as psychotropic or antimuscarinic drugs were coadministered, they may also occur with antipsychotic use alone. Signs related to atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, abdominal bloating, tachycardia and feeding disorder in neonates can also occur. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. Appropriate monitoring and treatment of neonates born to mothers receiving Piportil L_4 are recommended

Since the safety of Pipotil L4 during pregnancy has not been established, Piportil L_4 should not be used during pregnancy or in women of child bearing potential unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

PRECAUTIONS

Phenothiazines, particularly those that are long-acting, should be used with caution in patients with a history of convulsive disorders; treatment should not be initiated unless such patients are receiving appropriate anticonvulsive medication.

The increased incidence of seizures, which occasionally occur in epileptics started on antipsychotic medication, may be controlled by increasing the dosage of their anticonvulsant. Patients with a familial history of seizures or febrile convulsions are more likely to develop seizures than those who have no such history.

Hypotensive phenomena may develop in phenothiazine-treated patients who are undergoing surgery. Careful observation is necessary and dosages of anesthetics or central nervous system depressants may have to be reduced. Antipsychotic agents should be temporarily discontinued in patients receiving spinal or epidural anesthesia, if possible, to allow time for the residual drug to be metabolized.

Particularly during the first two or three months of therapy, it is advisable to perform periodic liver function tests and blood counts as cholestatic jaundice and blood dyscrasias may occur, necessitating discontinuation of treatment. During long-term therapy renal function should be monitored and, if BUN (blood urea nitrogen) becomes abnormal, treatment should be discontinued.

The effects of anticholinergic drugs may be potentiated by pipotiazine palmitate. Paralytic ileus, even resulting in death, may occur, especially in the elderly. Caution should be observed if constipation develops.

Retinal changes, lenticular and corneal deposits and abnormal skin pigmentation have been observed with other phenothiazines and may occur after prolonged therapy. The possibility of persistent tardive dyskinesia should also be borne in mind when patients are under long-term treatment.

Patients receiving pipotiazine palmitate should be cautioned against exposure to extreme heat or organophosphorous insecticides.

False positive or negative pregnancy tests have occurred in patients receiving phenothiazine therapy.

Hypotension and electrocardiographic changes, particularly non-specific and usually reversible Q and T wave distortions, have been associated with the administration of phenothiazines. Therefore, pipotiazine palmitate should be used with caution in patients with compensated cardiovascular and cerebrovascular disorders.

Neuroleptic phenothiazines may potentiate QT interval prolongation. QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e., drug induced) QT prolongation (See WARNINGS and ADVERSE REACTIONS).

The antiemetic effects of most phenothiazines can obscure toxic signs due to overdosage of other drugs or they may mask the symptoms of diseases such as brain tumors or intestinal obstruction.

Unexpected, sudden deaths have occurred in hospitalized patients treated with phenothiazines. Previous brain damage or seizures may predispose. High doses should be avoided in known seizure patients. Sudden exacerbations of psychotic behavior patterns occurred in several patients shortly before death. Acute fulminating pneumonia or pneumonitis and aspiration of gastric contents also were observed. Therefore, the physician also should keep in mind the possible development of "silent pneumonias".

Withdrawal Emergent Neurological Signs: Abrupt withdrawal after short-term administration of antipsychotic drugs does not generally pose problems. However, transient dyskinetic signs are experienced by some patients on maintenance therapy after abrupt withdrawal. The signs are very similar to those described under Tardive Dyskinesia, except for duration. Although it is not known whether gradual withdrawal of antipsychotic drugs will decrease the incidence of withdrawal emergent neurological signs, gradual withdrawal would appear to be advisable.

Blood disorders

Neutropenia, granulocytopenia and agrunulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting Piportil L_4 and then periodically throughout treatment.

Special Populations

Geriatric Patients: The incidence of adverse reactions may be greater in patients over 55 years of age, since the half-lives of antipsychotic drugs are often prolonged. To minimize this possibility, the maintenance dosage should be reduced to the lowest effective level as soon as possible after initial titration and periodically reviewed.

Since psychiatric syndromes in the elderly can be caused by drugs or organic disease, withdrawal of the precipitating drug or treatment of the medical condition should supersede initiation of antipsychotic medication. These agents should not be used for non-psychiatric conditions for which other drugs are available, since the elderly are especially prone to develop adverse effects from antipsychotic drugs.

Mortality in Geriatric Patients with Dementia-related Psychosis

In elderly patients with dementia-related psychosis, the efficacy and safety of Piportil L4 has not been studied. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Piportil L4 is not indicated for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Events (CVAEs) including stroke in Elderly Patients with Dementia

An increased risk of cerebrovascular adverse events has been seen in the dementia population in clinical trials with some atypical antipsychotics. The mechanism for this increased risk is not known. There is insufficient data to know if there is an increased risk of cerebrovascular events associated with Piportil L4. An increased risk however cannot be excluded. Piportil L4 is not indicated in elderly patients with dementia.

Vascular disease

Piportil L4 should be used with caution in patients with risk factors for stroke or with a history of stroke.

Endocrine and Metabolism

Hyperglycaemia or intolerance to glucose has been reported in patients treated with Piportil L_4. Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on Piportil L_4, should get appropriate glycaemic monitoring during treatment (See ADVERSE REACTIONS)].

Hyperprolactinemia
Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies, nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorogenesis; the available evidence is considered too limited to be conclusive at this time.

Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

ADVERSE REACTIONS

Neurological: The side effects most frequently reported are extrapyramidal reactions including tremor, rigidity, akathisia, dystonia, dyskinesia, oculogyric crises, opisthotonos, hyperreflexia and sialorrhea which tend to occur in the first few days after an injection of Piportil L_4 (pipotiazine palmitate) . Piportil L_4 tends to produce a higher incidence of extrapyramidal reactions than some other phenothiazine derivatives. Extrapyramidal reactions may be alarming, and the patient should be forewarned and reassured. These reactions may tend to subside as treatment is continued but are often dose-related and may respond to a reduction of the dose. Anti-parkinsonian medication may be required to control serious reactions or, if intractable, the drug may have to be withdrawn. The information available tends to indicate that persistent tardive dyskinesia results from heavy drug overloading of the extrapyramidal system. Therefore, caution should be exercised to avoid overdosing of Piportil L_4 and the optimum dosage should not be exceeded since this will tend to elicit marked extrapyramidal reactions.

Persistent Tardive Dyskinesia: As with other antipsychotic agents, tardive dyskinesia may occur in patients on long-term therapy or may be observed after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high doses, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the

tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes, these may be accompanied by involuntary movements of the extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop. The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptic drugs and reducing the dose or discontinuing the drug, if possible, when manifestations of this syndrome are recognized, particularly in patients over the age of 50.

Behavioral: Sleep disturbances, drowsiness, fatigue, insomnia, and depression have been reported and may, in severe cases, necessitate reduction in dosage. As with other phenothiazine derivatives, reactivation or aggravation of psychotic processes may be encountered.

Paradoxical effects such as agitation, anxiety, restlessness, excitement and bizarre dreams, have been observed in some patients.

Autonomic Nervous System: Dry mouth and nausea were most frequently seen during Piportil L_4 therapy. Tachycardia, hypotension, syncope, dizziness, blurred vision, vomiting, sweating, nasal congestion, and urinary incontinence have also been observed. Patients should be advised of the risk of severe constipation during Piportil L_4 treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

Patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to hypotensive reactions with phenothiazine compounds, and should therefore be observed closely when the drug is administered. Should hypotension occur in patients receiving Piportil L_4 and a vasopressor agent be required, i.v. norepinephrine or phenylephrine should be used, and not epinephrine, since phenothiazine derivatives can reverse the pressor effect of the latter drug.

Other autonomic reactions which have occurred with phenothiazines are salivation, polyuria, glaucoma, bladder paralysis, adynamic ileus, and fecal compaction.

Metabolic and Endocrine: Anorexia, menstrual irregularities, impotence, and increased thirst have been reported with Piportil L_4. Hyperglycaemia or intolerance to glucose has been reported in patients treated with Piportil L4. (See PRECAUTIONS).

Weight changes, increased appetite, peripheral edema, galactorrhea, gynecomastia and changes in libido have also occurred in patients receiving phenothiazine therapy.

Allergic or Toxic: Pruritus, dermatitis and rash have been observed with Piportil L_4. Other allergic reactions reported with phenothiazine derivatives are erythema, urticaria, seborrhea, eczema, exfoliative dermatitis, and photosensitivity. The possibility of an anaphylactoid reaction should be borne in mind.

Blood dyscrasias including leukopenia, granulocytopenia, neutropenia, agranulocytosis, pancytopenia, thrombocytopenic or non-thrombocytopetic purpura, eosinophilia, and anemia, have been associated with phenothiazine therapy. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting Piportil L_4 and then periodically throughout treatment. (See WARNINGS)

If any soreness of the mouth, gums or throat or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Cholestatic jaundice and biliary stasis may be encountered, particularly during the first months of therapy, and require immediate discontinuation of treatment.

Miscellaneous: The following adverse reactions have been reported in patients receiving phenothiazine derivatives: headache, asthma, laryngeal, cerebral and angioneurotic edema, altered cerebrospinal fluid proteins, systemic lupus erythematosus-like syndrome, hyperpyrexia, ECG and EEG changes and hypotension severe enough to cause fatal cardiac arrest. Skin pigmentation, epithelial keratopathy, lenticular and corneal deposits have been associated with long-term administration.

Very rare cases of QT interval prolongation have been reported. There have been isolated reports of sudden death, with possible causes of cardiac origin (see WARNINGS and PRECAUTIONS) as well as cases of unexplained sudden death have been reported in patients receiving neuroleptic phenothiazines.

Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs (see also WARNINGS).

Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown flare-ups of psychotic behaviour patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions.

Potentiation of CNS depressants (barbiturates, narcotics, analgesics, alcohol, antihistamines), may occur. Local tolerance to pipotiazine palmitate is good and reactions at the site of injection are seldom seen.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: In case of overdosage, severe extrapyramidal manifestations, hypotension, lethargy and sedation are most likely to be observed. Initial hospitalization may be required and close medical supervision should be maintained until symptoms are well under control.

Treatment: Treatment is essentially symptomatic and supportive. Severe extrapyramidal reactions may be treated with an appropriate antiparkinsonian agent. Maintain an adequate airway and, in cases of severe hypotension, administer i.v. norepinephrine or phenylephrine (not epinephrine as it may further depress the blood pressure).

When a sufficient amount of time has elapsed or when the patient shows signs of relapse, treatment may be resumed at a lower dosage.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Piportil L_4 (pipotiazine palmitate) is to be administered as an intramuscular injection only. Piportil L_4, as a long-acting depot phenothiazine, has been found useful in the maintenance therapy of non-agitated, chronic schizophrenic patients stabilized with shorter acting neuroleptics who might benefit from a transfer to a long-acting injectable drug.

The changeover to Piportil L_4 should aim at maintaining a clinical outcome similar to or better than that obtained with the previously used antipsychotic agent in patients who cannot be relied upon to take oral medication regularly. In those patients who might benefit from a long-acting neuroleptic, it is suggested to discontinue the previous antipsychotic medication prior to the changeover of drugs.

The initial dose and the intervals between injections should be selected on an individual basis, considering such factors as age, physical condition, symptoms and severity of illness, and previous drug history. Depending on the previous drug history and other individual factors, an initial dose of 50 mg to 100 mg may be administered. If necessary, further symptom control can usually be obtained by increasing the dose by increments of 25 mg every 2 or 3 weeks. The optimal dose and the interval between injections must be

determined in accordance with the patient's response. A single injection of Piportil L_4 may effectively control the schizophrenic symptoms for 3-6 weeks. However, it is frequently possible to achieve adequate control with a dosage between 75 and 150 mg administered every 4 weeks. Some patients may not require more than 25 to 50 mg every 4 weeks, while in others, doses of up to 250 mg may be needed.

Lower doses should be used in patients over the age of 50 when initiating therapy with Piportil L_4.

The dosage should not be increased in order to prolong the interval between injections. Some patients may benefit from the use of lower doses administered every 3 weeks. Regular and continuous supervision is considered essential in order to maintain the patient on the lowest effective individual dose and to make any additional adjustments in the dosage which may be required to avoid overdosage and troublesome adverse effects.

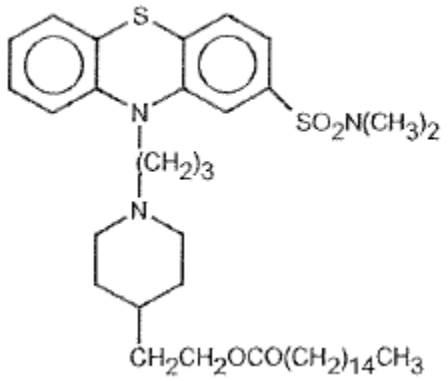
Although the incidence of extrapyramidal reactions is high, antiparkinsonian medication should be prescribed only to treat emergent symptoms that may occur. They should not be used prophylactically against such reactions.

A dry syringe and a needle of at least 21 gauge should be used to inject Piportil L_4. Use of a wet needle or syringe may cause the solution to become cloudy.

PHARMACEUTICAL INFORMATION

Chemically, pipotiazine palmitate is:
3-dimethysulphamoyl-10-[3-(4-palmitoyloxyethylpiperidino)propyl]phenothiazine

Its structural formula is



Molecular formula: $C_{40}H_{63}N_3O_4S_2$

Molecular weight: 714.1

Storage recommendation:
Store at room temperature (15 to 30°C) and protect from light.

AVAILABILITY OF DOSAGE FORMS

25 mg/mL injectable: Each mL contains: pipotiazine palmitate 25 mg. Non-medicinal ingredients: sesame oil. Ampoules of 1 mL, boxes of 5.

50 mg/mL injectable: Each mL contains: pipotiazine palmitate 50 mg. Non-medicinal ingredients: sesame oil. Ampoules of 1 mL, boxes of 5; ampoules of 2 mL, boxes of 5.

PHARMACOLOGY

In comparative studies with thioproperazine and fluphenazine, pipotiazine base exerted the following activity on the CNS:

			ED_{50} (mg/kg)		
Technique	Species	Route	Pipotiazine	Thioprperazine	Fluphenazine
Potentiation of hexobarbital narcosis	Mouse	p.o.	35	35	7.5
Hypothermic activity	Mouse	p.o.	35	100	7
Hypomotility	Mouse	p.o.	19	40	2
Traction	Mouse	s.c. p.o.	20 50	120 120	3.5 10
Fighting -footshock fighting -isolation fighting	Mouse Mouse	s.c. p.o. p.o.	3.5 10 10	2.5 15 40	0.7 0.9 4.5
Catalepsy	Mouse Rat	p.o. s.c. p.o.	5 1.5 7	6 1 6	1 0.4 1
Anti-amphetamine activity (stereotypies)	Rat	s.c. p.o.	0.30 4.5	0.15 2.5	0.07 0.65
Anti-apomorphine activity - stereotypies	Rat Dog	s.c. s.c. p.o.	0.45 0.002 0.013	0.50 0.003 0.005	0.1 0.013 0.045

In the dog, apomorphine-induced vomiting was inhibited for up to 56 days by a single dose (0.320 mg/kg s.c.) of pipotiazine palmitate.

In mice, at a dose of 25 mg/kg s.c., pipotiazine palmitate protected against dextroamphetamine toxicity for up to 14 days after its administration.

The stereotyped behavior (grooming and mouth movements) induced by amphetamine in rats was inhibited by pipotiazine palmitate for up to 49 days after a single administration. The minimal ED_{50} in this test was 4.3 mg/kg and the peak effect was observed after 2 or 3 days. Stereotyped mouth movements induced by apomorphine in the rats were inhibited

by pipotiazine palmitate (5 and 10 mg/kg s.c.), for about 13 days after injection.

In the pentobarbital anesthetized dog, pipotiazine palmitate (10 mg/kg i.m.) did not produce any significant effect on the cardiovascular and respiratory systems. The drug was devoid of anticholinergic effect and demonstrated only weak anti-adrenergic properties.

The pharmacokinetics of pipotiazine palmitate have been studied in rats and dogs by means of the H^3 labelled drug. It was shown that the drug was very slowly eliminated, some 50% of the administered radioactivity still being present in the organism after 20 to 30 days, while 10% still remained after 80 days. The half-life of pipotiazine palmitate was approximately 15 days, with the blood levels usually remaining constant over days 6 to 25 after the injection. It should be noted however, that at any time during the observation period, 95% of the total body radioactivity was present at the injection site, mainly in the form of pipotiazine palmitate. The drug is hydrolysed by blood and tissue esterases to pipotiazine, which is found at low concentrations in the blood, brain tissues, viscera and skin. The product undergoes enterohepatic recirculation and is mainly excreted in the feces, urinary elimination accounting for only about 10% of total excretion. Pipotiazine palmitate, pipotiazine base and pipotiazine sulfoxide only represent 2 to 7% of the total urinary excretion suggesting that, as with other phenothiazines, hydroxylated and glucuronide-conjugated derivatives may be the main metabolites found in the urine.

TOXICOLOGY

Acute Toxicity Studies

SPECIES	ROUTE	LD_{50} mg/kg
Mice	i.p.	> 1200
Rats	i.p.	> 500
Dogs	i.m.	> 200
Rabbits	i.m.	> 200

At the doses used, symptoms included heavy sedation, neuromuscular depression and growth retardation.

Subacute and Chronic Toxicity Studies

Species	Route	Dose (mg/kg/wk)	Duration	Findings
Rat	i.m.	0,1,3,9	2 months	Increased body weight gain in females.
Dog	i.m.	0,1,3,9	2 months	Increased SGPT at completion of study in one dog receiving 9 mg/kg/wk
Rat	i.m.	0,2.5,5,15	18 months	Reduced food intakes and body weight gains at the two higher dose levels. Increased body weight gain in females receiving 2.5 mg/kg/wk. Reduced weights of uteri and, in males only, of the liver at all dose levels. Increased pituitary weights in both sexes. Benign mammary gland tumours in 4/30 males at the 15 mg/kg/wk dose level" Injection sites showed swelling, especially in males.
Dog	i.m.	0,2.5,5,15	12 months	Increased body weight gain and body fat (not dose-related). Minimal congestion of mucosal surface at the entrance of ureters into the bladder of several animals. Reduced weights of prostate, testes and ovaries. Reduces weights of uteri at the two higher dose levels. Histologic evidence of delayed maturation of prostates in males, and of ovaries, uteri and mammary glands in females. Injection sites showed occasional pale interstitial "foamy" areas.

Reproduction studies:

Species	Sex	Dose (mg/kg)	Route	Times of administration	Findings
Mouse	F	0, 10, 20, 40	s.c.	Days 4, 7, 10 and 13 of gestation	No teratogenic or embryotoxic activities. Intrauterine growth and post-natal development were normal.
Rat	M	0, 2.5, 5, 15	i.m.	Weekly for 11 weeks: prior to mating and throughout mating period	Decreased fertility at 5 mg/kg/wk; this effect was not dose-related and the fertility index remained within the normal range
Rat	F	0, 0.5, 2.5, 5, 15	i.m.	Weekly for 2 weeks prior to mating, through mating gestation and lactation	At 2.5 mg/kg/wk and more, alterations in oestrous cycles with development of permanent dioestrous; the fertility index was decreased. Some fetal toxicity at the two highest dose levels.
Rat	F	0, 10, 20, 40	i.m.	Days 4, 7, 10 and 13 of gestation	No teratogenic or embroytoxic activities.
Rat	F	0, 2.5, 5, 15	i.m.	Days 14 and 21 of gestation and days 7 and 14 of lactation	No changes ween with regard to general behavior and appearance, body weight or survival of young, mean gestational length and mean number of young born per litter.

Species	Sex	Dose (mg/kg)	Route	Times of administration	Findings
Rabbit	F	0, 5, 10, 20	i.m.	Days 4, 7, 10 and 13 of gestation	No teratogenic effect. Increased resorption rate and slight inhibition of intrauterine fetal growth at the two higher dose levels.

Carcinogenicity Studies:

Species	Route	Dose (mg/kg/wk)	Duration	Findings
Mice	s.c.	0, 5, 10	18 months	Decreased weight gain in males receiving 15 mg/kg/wk during the frist 15 months of treatment. Decreased survival rate in females. Histopathological findings included increased incidences of pipuitary adenomas in both males and females, mammary gland adenocarcinomas and fibrocystic disease in females and non-noeplastic changes in the seminal vesicles (dilation and chronic inflammation), decreased incidences of lymphosarcoma in both sexes and age-related changes in ovaries of treated females.

Species	Route	Dose (mg/kg/wk)	Duration	Findings
Rats	i.m.	0, 5, 15	21 months followed by a 3-month treatment-free period.	Decreased weight gains in males at both dose levels and in high dose females. At the 15 mg/kg/wk dose, increased number of males with pituitary adenomas and of males and females with chronic inflammation of bile ducts; at the 5 mg/kg/wk dose, increased number of females with fibrocystic disease and intestinal calcification and of males with chronic inflammation of seminal vesicles at both dose levels, increase in the number of females with calcification in the lungs and of males with calcification in the kidney and thyroid, paw ulceration, adrenal hematocysts, chronic inflammation of prostate and mammary fibrocystic disease; treated females had dose-related decreases in hematocrit at 24 months; high-dose females had decreased hematocrit and erythrocytes at 21 months and a significant decrease in erythrocytes and hemoglobin at 24 months - most values were within the normal range.

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IMPORTANT: PLEASE READ

CONSUMER INFORMATION

PrPIPORTIL® L_4
pipotiazine palmitate injection

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Piportil L_4. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Piportil L_4 is used in adults to treat symptoms of chronic schizophrenias without agitation.

What it does:

Piportil L_4 helps reduce and control the symptoms of schizophrenia.

When it should not be used:

Do not use Piportil L_4 if you:

- Are allergic to Piportil L_4 to phenothiazines (a type of antipsychotic) or to any of the ingredients in the product (see the section "**What the non-medicinal ingredients are"**)
- Have a sudden blood circulation failure or are in an altered state of consciousness or coma, especially if these were caused by alcohol or drugs
- Suffer from severe depression
- Have liver disease
- Have a blood disorder
- Have kidney problems
- Have pheochromocytoma (a tumour of the adrenal gland)
- Have severe heart or blood vessel disorders
- Have or have had brain damage
- Are taking high doses of drugs that cause you to sleep

Piportil L_4 is not indicated for use in children or in elderly patients with dementia (mental decline).

What the medicinal ingredient is:

Pipotiazine palmitate

What the nonmedicinal ingredients are:

Sesame oil

What dosage forms it comes in:

Formulations for injection in the muscle

- 25 mg/mL
- 50 mg/mL

WARNINGS AND PRECAUTIONS

At the beginning of treatment, Piportil L_4 may cause some people to become drowsy or less alert. You should not drive a car, operate machinery or participate in activities requiring alertness until you are sure Piportil L_4 does not affect you.

You should use extra care not to be exposed to extreme heat or some type of insecticides. Check with your doctor or pharmacist.

Patients over 55 years of age are at greater risk to develop adverse effects.

If you experience severe constipation and you are elderly, please consult your doctor as soon as possible.

Muscular, neurologic, cardiac, vascular, eye, skin or respiratory problems and hyperglycaemia may occur in some patients taking Piportil L_4 (see the section **"SIDE EFFECTS AND WHAT TO DO ABOUT THEM"**).

Effects on Newborns:
In some cases, babies born to a mother taking Piportil L_4 during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

Before using Piportil L_4, tell your doctor if you:
- Have heart or blood vessel disease

- Have a history of cerebrovascular disease including strokes or transient ischemic attacks (mini-strokes)
- Have constipation or intestinal blockage
- Have or have had a brain tumour or brain damage
- Have or have had seizure disorders (e.g. epilepsy or have members of your family with seizure disorders)

- Have or have had breast cancer
- Plan to have surgery (or a procedure requiring anaesthetics)
- Are or are planning to become pregnant
- Are breast feeding

Occasional liver and blood function tests should be done while you are taking Piportil L_4, and kidney function tests should be done if you are taking it long-term.

INTERACTIONS WITH THIS MEDICATION

Piportil L_4 can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on Piportil L_4 therapy.

Before using any prescription, over-the-counter medicines or herbal products, check with your doctor or your pharmacist.

Piportil L_4 can add to the effects of other drugs that cause drowsiness. Some examples of drugs that can cause drowsiness are:

- Drugs for allergies
- Drugs for sleep
- Drugs for pain
- Drugs for seizure
- Drugs for depression
- Drugs for mental illness

Piportil L_4 may cause a false reading of some types of pregnancy tests. For further information, please consult your doctor or your pharmacist.

PROPER USE OF THIS MEDICATION

Usual dose:

Piportil L_4 is given by an injection in the muscle.

- Your doctor has decided the best dose for you based on your individual situation and needs.

An initial dose of 50 mg to 100 mg may be given. Your doctor may decide to start your treatment with lower doses, particularly if you are over 50 years old.
If needed, your doctor may increase your dose usually by 25 mg every 2 or 3 weeks.

Based on your response, your doctor will determine your dose and the interval between the injections.

You may experience side effects if the drug is stopped suddenly. Contact your physician before stopping your drug.

Overdose:

The signs if you have received too much Piportil L_4 may include, spasm, muscle stiffness, tremor, impairment of voluntary movement, weakness, drowsiness and low blood pressure.

If you have received too much Piportil L_4, immediately see your doctor or go to your nearest hospital emergency department or contact your Regional Poison Centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Piportil L_4, like any medication, may cause some side effects. Discuss with your doctor if you do experience side effects.

Reactions at the site of injection are seldom seen.

Side effects include:

- Appetite change, constipation, dryness of the mouth, increase thirst, nasal congestion, nausea, urinary incontinence, sweating, vomiting, weight change.
-
- Agitation, anxiety, bizarre dreams, dizziness, excitement, restlessness.
- Changes in libido, increase of the breast size in men, impotence, lactation, menstrual irregularities,

peripheral oedema (swelling

- of the legs, ankles, and feet)
- Your skin may be more sensitive to sunlight.

Side effects that might need a reduction in your dose are:
Drowsiness, fatigue, insomnia, sad mood, sleep disturbances.

Your doctor should check your body weight before starting Piportil L_4 and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting Piportil L_4. They will monitor blood sugar, and the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism, you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

This is not a complete list of side effects. For any unexpected effects while taking Piportil L_4, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 to 30^{o} C). Protect from exposure to light.

Keep in a safe place out of the reach of children.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN ANDWHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency assistance
	Only if severe	In all cases	
Common			
Muscle stiffness, body spasm, impairment of voluntary movement, upward eye rolling, exaggeration of reflexes or drooling			x
Uncommon			
Allergic reaction such as skin rash, redness or itching			x
Respiratory infection, fever, flu-like symptoms, coughing, difficult or fast breathing			x
Soreness of the mouth, gums or throat, abdominal pain or jaundice			x
Rapid or irregular heart beat, low or high blood pressure			x
Blurred vision, or other eye disorder		x	
Increased sweating confusion, reduced consciousness			x
Muscle twitching or abnormal movement of the face or tongue		x	
Pain, swelling , redness or warmth in arms or legs, chest pain, anxiety, coughing up blood		~~x~~	x
Hyperglycaemia (too much sugar in the blood) with symptoms such as increased thirst, decreased appetite, nausea or vomiting		x	
Long-lasting (greater than 4 hours in duration) and painful erection of the penis			x
New or worsening constipation		x	

IMPORTANT: PLEASE READ

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701 E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect .

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Your physician, nurse and pharmacist are always your best source of information about your condition and treatment. If you have additional questions or concerns, be sure to ask them.

This document plus the full product monograph is available at www.sanofi-aventis.ca or upon request to the sponsor, sanofi-aventis Canada Inc., 2150 St Elzear Blvd. West , Laval , Quebec H7L 4A8, at: 1-800-265-7927

This leaflet was prepared by sanofi-aventis Canada Inc.

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