

DATASHEET

PIPORTIL

NAME OF THE MEDICINE

Pipothiazine palmitate 50 mg/ml injection

PRESENTATION

Injection (in sesame oil) 50 mg/ml; straw-coloured viscous liquid.

USES

Actions

Pipothiazine palmitate is an oil-soluble ester of pipothiazine, a piperidine-type phenothiazine. The esterification of pipothiazine is responsible for its prolonged duration of action on deep intramuscular injection there is slow diffusion of the ester from the oily depot into tissue where it is hydrolysed to the active parent drug, pipothiazine.

PIPORTIL DEPOT possesses a wide range of antipsychotic activity, a weak sedative action, a high degree of tolerance, and an average duration of action of 4 weeks. It has a potent activity against the major symptoms of chronic schizophrenia such as hallucinations and delusions, and is also effective against negative symptoms such as emotional withdrawal, unco-operativeness and other residual symptoms which interfere with social integration.

The onset of action appears usually within 2 to 3 days after injection and the effects of the medicine on psychotic symptoms may be noted within 2 weeks. Improvement in symptomatology lasts from 3 to 6 weeks, but adequate control is frequently maintained with one injection every 4 weeks. However, in view of the variations in individual response, careful supervision is required throughout treatment.

Pharmacokinetics

There is little information about blood levels, distribution and excretion in humans. The rate of metabolism and excretion of phenothiazines decreases in old age.

INDICATIONS

PIPORTIL DEPOT is a long-acting phenothiazine neuroleptic indicated for the maintenance treatment of schizophrenia and paranoid psychoses, and prevention of relapse, especially where compliance with oral medication is a problem.

CONTRAINDICATIONS

PIPORTIL DEPOT should not be administered to patients in comatose states or with marked cerebral atherosclerosis, phaeochromocytoma, renal or liver failure, severe cardiac insufficiency or hypersensitivity to other phenothiazine derivatives.

PRECAUTIONS

PIPORTIL DEPOT should be used with caution in patients suffering from or who have a history of, the following conditions: severe respiratory disease, epilepsy, alcohol withdrawal symptoms, brain damage, Parkinson's disease or marked extrapyramidal symptoms with previously used neuroleptics, personal or family history of narrow angle glaucoma, hypothyroidism, myaesthesia gravis, prostatic hypertrophy, thyrotoxicosis. Care is required in very hot or very cold weather particularly in elderly frail patients.

As with other neuroleptics, very rare cases of QT interval prolongation have been reported. 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 **ADVERSE EFFECTS**).

An increased risk of cerebrovascular events has been reported in elderly patients with dementia treated with atypical antipsychotic drugs. An increase in the risk of cerebrovascular events with other antipsychotic drugs or other populations of patients cannot be excluded. PIPORTIL DEPOT should therefore be used with caution in patients with stroke risk factors.

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, PIPORTIL DEPOT should be used with caution in patients with risk factors for thromboembolism (see **ADVERSE EFFECTS**).

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Although the causes of death in clinical trials with atypical antipsychotics 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.

Hyperglycaemia or intolerance to glucose has been reported in patients treated with PIPORTIL DEPOT. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on PIPORTIL DEPOT, should get appropriate glycaemic monitoring during treatment (see **ADVERSE EFFECTS**).

Use In Pregnancy

Category C

The medicine should not be used during pregnancy or lactation unless the physician considers it essential.

The following effects have been reported (in postmarketing surveillance) in neonates exposed to phenothiazines during the third trimester of pregnancy:

- various degrees of respiratory disorders ranging from tachypnoea to respiratory distress, bradycardia and hypotonia, most often when other drugs such as psychotropic or antimuscarinic drugs were coadministered.

- signs related to the atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, initial feeding difficulties, abdominal bloating, tachycardia;
- neurological disorders such as extrapyramidal symptoms including tremor and hypertonia, somnolence, agitation.

Appropriate monitoring and treatment of neonate born to mothers receiving PIPORTIL DEPOT is recommended.

ADVERSE EFFECTS

Minor side effects of neuroleptics are nasal stuffiness, dry mouth, insomnia, agitation and weight gain. Other possible adverse effects are listed below.

Liver Function

Jaundice, usually transient, occurs in a very small percentage of patients taking neuroleptics. A premonitory sign may be a sudden onset of fever after one to three weeks of treatment followed by the development of jaundice. Neuroleptic jaundice has the biochemical and other characteristics of obstructive jaundice and is associated with obstructions of the canaliculi by bile thrombi, the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment should be withheld on the development of jaundice.

Cardiorespiratory

Hypotension, usually postural, commonly occurs. Elderly or volume depleted subjects are particularly susceptible; it is more likely to occur after intramuscular administration.

Cardiac arrhythmias, including atrial arrhythmia. A-V block, ventricular tachycardia and fibrillation have been reported during neuroleptic therapy, possibly related to dosage. Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose.

ECG changes, usually benign, include QT interval prolongation, ST depression, U-waves and T-wave changes.

There have been isolated reports of sudden death, with possible causes of cardiac origin (see **PRECAUTIONS**), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Respiratory depression is possible in susceptible patients.

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

Blood Picture

A mild leucopenia occurs in up to 30% of patients on prolonged high dosage of neuroleptics. Agranulocytosis may occur rarely, it is not dose related. The occurrence of unexplained infections or fever requires immediate haematological investigation.

Extrapyramidal

Acute dystonias or dyskinesias, usually transitory, are more common in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.

Akathisia characteristically occurs after large initial doses.

Parkinsonism is more common in adults and the elderly. It usually develops after weeks or months of treatment. One or more of the following may be seen: tremor, rigidity, akinesia or other features of Parkinsonism. Commonly just tremor.

Tardive Dyskinesia

If this occurs it is usually, but not necessarily, after prolonged or high dosage. It can even occur after treatment has been stopped. Dosage should therefore be kept low whenever possible.

Skin and Eyes

Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of phenothiazines, the greatest care must be taken to avoid contact of the medicine with the skin. Skin rashes of various kinds may also be seen in patients treated with these medicines.

Patients on too high a dose should be warned that they may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight.

Ocular changes and the development of metallic greyish-mauve colouration of the exposed skin have been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (four to eight years). Other neuroleptics have been implicated but less frequently.

Endocrine

Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea, impotence.

Hyperglycaemia

In post-marketing surveillance cases of intolerance to glucose, hyperglycaemia have been reported (see **PRECAUTIONS**).

Neuroleptic malignant syndrome Hyperthermia, rigidity, autonomic dysfunction and altered consciousness may occur with any neuroleptic.

INTERACTIONS

Caution is required with the use of the following medicines due to the risk of QT prolongation (see **PRECAUTIONS**):

- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as bepridil, cisapride, sultopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.
- Medicines which induce bradycardia, such as bradycardia-inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, guanfacine, digitalis.
- Medicines which can cause hypokalaemia, such as diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides.

- Other antipsychotics .

Interactions of phenothiazine neuroleptics

The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, barbiturates, and other sedatives. Respiratory depression may occur.

The hypotensive effect of most antihypertensive medicines especially alpha-adrenoceptor blocking agents may be exaggerated by neuroleptics.

The mild anticholinergic effect of neuroleptics may be enhanced by other anticholinergic medicines possibly leading to constipation and even paralytic ileus, heat stroke, etc.

The action of some agents may be opposed by phenothiazine neuroleptics. These include amphetamine, levodopa, clonidine, guanethidine, adrenaline.

Anticholinergic agents may reduce the antipsychotic effect of neuroleptics.

Some medicines interfere with absorption of neuroleptic agents: antacids, antiparkinson, lithium.

Increases or decreases in the plasma concentrations of a number of agents, e.g. propranolol, phenobarbitone have been observed but were not of clinical significance.

High doses of neuroleptics reduce the response to hypoglycaemic agents, the dosage of which might have to be raised. Adrenaline must not be used in patients overdosed with phenothiazine neuroleptics. Most of the above interactions are of a theoretical nature and not dangerous.

DOSAGE AND ADMINISTRATION

Patients should be stabilised on PIPORTIL DEPOT under psychiatric supervision. Administration should be by deep intramuscular injection into the gluteal region.

Adults

Initially 25 mg (0.5 ml) should be given to assess the response of the patient to the medicine. Further doses should be administered at appropriate intervals, increasing by increments of 25 or 50 mg until a satisfactory response is obtained. In clinical practice PIPORTIL DEPOT has been shown to have a long duration of action, allowing intervals of 4 weeks between injections for maintenance therapy. Dosage should be adjusted under close supervision to suit each individual patient in order to obtain the best therapeutic response compatible with tolerance.

The duration of action depends on dose administered, allowing dosage intervals to be varied to suit individual circumstances.

Most patients respond favourably to a dose of 50-100 mg (1-2 ml) every 4 weeks. The maximum recommended dose is 200 mg (4 ml) every four weeks.

Elderly

Neuroleptics should be used cautiously in the elderly, a reduced starting dose is recommended, i.e. 5-10 mg might be considered.

Children

Not recommended for use in children.

OVERDOSE

Symptoms of phenothiazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, ECG changes, ventricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesias may occur.

Generalised vasodilatation may result in circulatory collapse raising the patient's legs may suffice. In severe cases, volume expansion by intravenous fluids may be needed. Infusion fluids should be warmed before administration in order not to aggravate hypothermia.

Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstrictor agents are not generally recommended, avoid the use of adrenaline.

Ventricular or supraventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If they are persistent or life threatening, appropriate anti-arrhythmic therapy may be considered. Avoid lignocaine and, as far as possible, long acting anti-arrhythmic agents.

Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5-10 mg) or orphenadrine (20-40 mg) administered intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam.

Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

PRESENTATION AND STORAGE CONDITIONS

Injection 50 mg/ml, 1 ml and 2 ml, 10s.

PIPORTIL DEPOT should be protected from light. It can be stored at room temperature.

FURTHER INFORMATION

PIPORTIL DEPOT contains sesame oil to 100ml.

MEDICINES CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF SPONSOR

sanofi-aventis new zealand limited
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56 Cawley Street
Ellerslie

Auckland
New Zealand

DATE OF PREPARATION

22 August 2011