

1. NAME OF THE MEDICINAL PRODUCT

Fluphenazine Decanoate Injection BP 25mg/ml, 0.5ml, 1ml & 2ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains Fluphenazine Decanoate BP 25mg.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear light yellow sterile solution.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

Fluphenazine decanoate is a long-acting antipsychotic agent. It is intended for use in the management of patients who require prolonged parenteral therapy with a neuroleptic drug, such as patients with schizophrenia and those with paranoid psychoses.

Fluphenazine decanoate should be administered by deep intramuscular injection.

4.2. Posology and method of administration

Fluphenazine decanoate should be given by deep intramuscular injection. It is preferable that patients be stabilised on fluphenazine decanoate therapy in hospital. The onset of action is usually 1 to 3 days and significant effects on psychotic symptoms are usually evident within 2 to 4 days.

Adults:

Patients receiving a depot preparation of fluphenazine for the first time may be given 12.5mg (0.5ml) initially (this dose should be halved for patients over 60 years) by deep I.M. injection into the gluteal region. The subsequent doses and between-dose intervals will depend on the patients' response, most patients being successfully maintained within a dose range of 12.5 to 100mg given at a dose interval of between 2 to 5 weeks.

Patients resuming therapy with a depot preparation of fluphenazine may be given the same dose as they were receiving prior to discontinuation of treatment, although the frequency of injections may need to be increased in the early weeks of treatment until adequate control is achieved.

Patients previously maintained on oral fluphenazine: In view of the wide variability in individual response, it is not possible to predict the equivalent dose of depot injection form.

Elderly:

A smaller initial dose (see above) should be used and smaller maintenance doses may be required for elderly patients, in view of their increased susceptibility to extrapyramidal effects.

Children:

Not recommended for children.

4.3. Contraindications

Comatose and severely depressed states.

Hepatic or renal failure.

Severe cardiovascular or cerebro-vascular insufficiency. Marked cerebral atherosclerosis

Phaeochromocytoma.

Patients with existing blood dyscrasias.

Hypersensitivity to fluphenazine and any of the ingredients.

4.4. Special warnings and precautions for use

Particular care is required when using fluphenazine in any of the following conditions:

Liver disease; Renal Impairment cardiac disease or the presence of cardiac arrhythmias; thyrotoxicosis; severe respiratory disease; epilepsy or conditions predisposing to epilepsy, such as alcohol withdrawal or brain damage; Parkinson's disease; patients with a history of hypersensitivity to other phenothiazines; personal or family history of narrow angle glaucoma; very hot weather or where the ambient temperature is high; the elderly, especially if frail or at risk of hypothermia; hypothyroidism; myasthenia gravis; prostatic hypertrophy.

Patients with known or with a family history of cardiovascular disease should receive ECG screening, and monitoring and correction of electrolyte balance prior to treatment with fluphenazine.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Fluphenazine and preventive measures undertaken.

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement

disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Psychotic patients on large doses of phenothiazines who are undergoing surgery should be watched carefully for hypotension. Reduced amounts of anaesthetics or central nervous system depressants may be necessary.

Fluphenazine should be used with caution in patients exposed to organophosphorus insecticides

Neuroleptic drugs elevate prolactin levels, and an increase in mammary neoplasms has been found in rodents after chronic administration. However, studies to date have not shown an association between chronic administration of these drugs and human mammary tumours.

As with any phenothiazine, the physician should be alert to the possibility of “silent pneumonias” in patients receiving long-term fluphenazine.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Fluphenazine is not licensed for the treatment of dementia-related behavioural disturbances.

4.5. Interaction with other medicinal products and other forms of interaction

The possibility should be borne in mind that phenothiazines may:

1. Increase the CNS-depressant effects of drugs such as alcohol, general anaesthetics, hypnotics, sedatives or strong analgesics.
2. Antagonise the action of sympathomimetic agents, including adrenaline and reverse the blood-pressure lowering effects of adrenergic-blocking agents such as guanethidine and clonidine.
3. Impair the anti-Parkinsonian effect of L-dopa, the effect of anticonvulsants, the metabolism of tricyclic antidepressants and the control of diabetes mellitus.
4. Increase the effect of anticoagulants and antidepressants.
5. Interact with lithium.
6. Enhance the anticholinergic effects of other anticholinergic drugs, including the antimuscarinic anti-Parkinsonian agents. Phenothiazines may enhance: the absorption of corticosteroids, digoxin and neuromuscular blocking agents.

Fluphenazine is metabolised by P450 2D6 and is itself an inhibitor of this drug metabolising enzyme. The plasma concentrations and the effects of fluphenazine may therefore be increased and prolonged by drugs that are either the substrates or inhibitors of this P450 isoform, possibly resulting in severe hypotension, cardiac arrhythmias or CNS side effects. Examples of drugs which are substrates or inhibitors of cytochrome P450 2D6 include anti-arrhythmics, certain antidepressants including SSRIs and tricyclics, certain antipsychotics, β -blockers, protease inhibitors, opiates, cimetidine and ecstasy (MDMA). This list is not exhaustive.

Concomitant use of barbiturates with phenothiazines may result in reduced serum levels of both drugs, and an increased response if one of the drugs is withdrawn.

The effect of fluphenazine on the QT interval is likely to be potentiated by concurrent use of other drugs that also prolong the QT interval. Therefore, concurrent use of these drugs and fluphenazine is contraindicated. Examples include certain anti-arrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone and sotalol), tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as phenothiazines and pimozide); certain antihistamines (such as terfenadine); lithium, quinine, pentamidine and sparfloxacin. This list is not exhaustive.

Electrolyte imbalance, particularly hypokalaemia, greatly increases the risk of QT interval prolongation. Therefore, concurrent use of drugs that cause electrolyte imbalance should be avoided.

Concurrent use of MAO inhibitors may increase sedation, constipation, dry mouth and hypotension.

Owing to their adrenergic action, phenothiazines may reduce the pressor effect of adrenergic vasoconstrictors (i.e. ephedrine, phenylephrine).

Phenylpropanolamine has been reported to interact with phenothiazines and cause ventricular arrhythmias.

Concurrent use of phenothiazines and ACE inhibitors or angiotensin II antagonists may result in severe postural hypotension.

Concurrent use of thiazide diuretics may cause hypotension. Diuretic-induced hypokalaemia may potentiate phenothiazine-induced cardiotoxicity.

Clonidine may decrease the antipsychotic activity of phenothiazines.

Methyldopa increases the risk of extrapyramidal side effects with phenothiazines.

The hypotensive effect of calcium channel blockers is enhanced by concurrent use of antipsychotic drugs.

Phenothiazines may predispose to metrizamide-induced seizures.

Concurrent use of phenothiazines and amphetamine/anorectic agents may produce antagonistic pharmacological effects.

Concurrent use of phenothiazines and cocaine may increase the risk of acute dystonia.

There have been rare reports of acute Parkinsonism when an SSRI has been used in combination with a phenothiazine.

Phenothiazines may impair the action of anti-convulsants. Serum levels of phenytoin may be increased or decreased.

Phenothiazines inhibit glucose uptake into cells, and hence may affect the interpretation of PET studies using labelled glucose.

4.6. Pregnancy and lactation

Because the safe use of fluphenazine in pregnancy has not been established, the possible risks should be weighed against the potential benefits when considering its usage in patients who are pregnant. Breast feeding should be avoided because of the possibility that fluphenazine is excreted in breast milk.

4.7. Effects on ability to drive and use machines

Fluphenazine may impair the mental or physical abilities required for driving a car or operating machinery.

4.8. Undesirable effects

Acute dystonic reactions may occur, infrequently, and are more likely to manifest within the first 24 to 48 hours, although delayed reactions may occur. They may include oculogyric crises and opisthotonus and, in susceptible individuals, may occur after only small doses. Such reactions may be rapidly relieved by intravenous administration of an anti-Parkinsonian agent such as procyclidine.

Parkinsonian-like states may occur, particularly between the second and fifth days after each injection, but they often diminish with subsequent injections. These reactions may be reduced by dose reduction, or by concomitant use of anti-parkinsonian agents such as benhexol or procyclidine. However, anti-parkinsonian drugs should not be used routinely because of the possibility of anticholinergic side-effects, or the risk of precipitating toxic confusional states or of impairing therapeutic effect.

With careful monitoring to ensure that the smallest effective dose is used, the number of patients requiring anti-parkinsonian drugs can be minimised.

Tardive dyskinesia: as with all antipsychotic drugs, tardive dyskinesia may occur in some patients on long term therapy or may occur after drug therapy has been

discontinued. There appears to be a greater risk in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible.

Tardive dyskinesia is characterised by rhythmical involuntary movements of the tongue, face, mouth or jaw, such as protrusion of tongue, puffing of cheeks, puckering of mouth or chewing movements. There may be accompanying involuntary movements of the extremities.

There is no known effective treatment for tardive dyskinesia; anti-parkinsonian agents usually do not alleviate the symptoms. If these symptoms appear, it is suggested that where possible, all antipsychotic agents be discontinued. Where it becomes necessary to recommence therapy, or increase the dosage of the drug, or change to a different neuroleptic drug, 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. As with other phenothiazines, drowsiness, lethargy, blurred vision, dry mouth, constipation, urinary hesitancy or incontinence, mild hypotension, impairment of judgement and of mental skills and epileptiform attacks are occasionally seen.

Headache, nasal congestion, vomiting, agitation, excitement and insomnia, and hyponatraemia have been observed during phenothiazine therapy.

Blood dyscrasias have rarely been reported with phenothiazine derivatives. Full blood counts should be performed if there are signs of persistent infection. Transient leucopenia and thrombocytopenia have been reported. Antinuclear antibodies and SLE have been reported very rarely.

Jaundice has been reported rarely: transient abnormalities of liver function tests may occur in the absence of jaundice.

A transient increase in serum cholesterol has been reported very occasionally in patients receiving oral fluphenazine.

Abnormal skin pigmentation and lens opacities have sometimes been seen after long term use of high doses of phenothiazines.

Phenothiazines are known to cause photosensitivity reactions but this has not been reported for fluphenazine. Skin rashes, hypersensitivity and anaphylactic reactions have occasionally been reported.

Elderly patients may be more susceptible to the sedative and hypotensive effects.

The effects of phenothiazines on the heart are dose-related. ECG changes with prolongation of the QT interval and T-wave changes, have been reported commonly in patients receiving moderate to high dosage and are reversible on reducing the dose. In a very small number of patients, these changes have been reported to precede serious arrhythmias, including ventricular tachycardia and fibrillation, which have also occurred after overdosage. Sudden, unexpected and

unexplained deaths have been reported in hospitalised psychotic patients receiving phenothiazines.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs- Frequency unknown.

Phenothiazines may impair body temperature regulation and severe hypo- or hyperthermia have been reported in association with moderate or high dosage. Elderly or hypothyroid patients may be particularly susceptible to hypothermia. The risk of hyperthermia may be increased by very hot or humid weather or by drugs that impair sweating, such as anti-parkinsonian agents.

There have been rare occurrences of neuroleptic malignant syndrome (NMS) reported in patients receiving neuroleptic drugs. The syndrome is characterised by hyperthermia, together with some or all of the following: muscle rigidity, autonomic instability (labile B.P., tachycardia, diaphoresis) akinesia, altered consciousness, sometimes progressing to stupor or coma. Leucocytosis, raised CPK levels, liver function abnormalities and acute renal failure may also occur. If signs of this syndrome develop, neuroleptic therapy should be discontinued immediately and intensive symptomatic treatment implemented since the syndrome is potentially fatal.

The hormonal effect of phenothiazines include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligomenorrhoea- or amenorrhoea. Sexual function may be impaired and false results may be observed with pregnancy tests. Syndrome of inappropriate anti-diuretic hormone secretion has also observed.

Oedema has been reported in association with phenothiazine therapy.

4.9. Overdose

The expected symptoms of overdosage would be an exaggeration of the known pharmacological effects of fluphenazine and might therefore include extrapyramidal reactions, hypotension and excessive sedation.

There is no specific antidote to fluphenazine and treatment of overdose is symptomatic and supportive.

Severe extra-pyramidal reactions should be treated with an oral or parenteral anti-parkinsonian agent such as procyclidine or benztropine.

In cases of severe hypotension, all procedures for the management of circulatory shock should be instituted, eg. vasoconstrictors and/or intravenous fluids. If a vasoconstrictor is required, metaraminol or noradrenaline should be used; adrenaline should be avoided as it may further lower the blood pressure through interaction with the phenothiazine.

A patent airway should be established and respiratory depression may be managed by artificial respiration.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Fluphenazine is a phenothiazine derivative of the piperazine type. Fluphenazine decanoate is an ester of fluphenazine. The ester is slowly absorbed from the intramuscular site of injection, and is then hydrolysed in the plasma to the active agent, fluphenazine.

Although the mode of action is unknown, antagonism of dopamine-mediated central synaptic transmission may be the primary action through which fluphenazine exerts its antipsychotic effect.

Extrapyramidal reactions are not uncommon, but fluphenazine does not have pronounced sedative or hypotensive properties.

5.2. Pharmacokinetic Properties

Fluphenazine decanoate undergoes slow absorption from the site of intramuscular injection and is hydrolysed to release fluphenazine. Fluphenazine is extensively metabolised in the liver and excreted in the urine and faeces as unchanged drug and metabolites.

Plasma level profiles of fluphenazine from fluphenazine decanoate injection have shown half-lives of plasma clearance ranging from 2.5 to 16 weeks; this emphasises the importance of adjusting the dose and dose interval to the individual requirements of each patient. Because of the slow decline of plasma levels in most patients, a reasonably stable plasma level can usually be achieved with injections spaced at 2 to 4 week intervals.

5.3. Preclinical Safety Data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 Pharmaceutical Particulars

6.1. List of excipients

Sesame Oil Ph. Eur.

6.2. Incompatibilities

Do not mix with any other agent.

6.3. Shelf life

3 years (36 months).

6.4. Special precautions for storage

Keep in outer carton.
Do not store above 25°C.
Do not refrigerate.
Keep out of the reach of children.

6.5. Nature and contents of container

0.5ml, 1ml and 2ml clear glass ampoules, glass type I Ph. Eur. borosilicate glass packed in cardboard cartoons to contain

10 x 0.5ml; 10 x 1ml; 10 x 2ml; 5 x 0.5ml; 5 x 1ml; 5 x 2ml ampoules.

6.6. Special precautions for disposal

If only part of the contents of an ampoule is used, the remaining solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.,
Roscrea,
Co. Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER (S)

PL 02848/0132

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th October 1989.
Date of last renewal: 26th January 1995.

10. DATE OF REVISION OF THE TEXT

04 August 2010