SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Modecate Injection 25mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 25mg/ml of the active substance Fluphenazine Decanoate.

Also contains sesame oil (q.s.).

Benzyl alcohol 15 mg/ml.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
Pale yellow clear, oily liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment and maintenance of schizophrenic patients and those with paranoid psychoses.

While Modecate injection has been shown to be effective in acute states, it is particularly useful in the maintenance treatment of chronic patients who are unreliable at taking their oral medication, and also of those who do not absorb their oral phenothiazine adequately.

4.2 Posology and method of administration

Dosage and Administration

Adults

It is recommended that patients be stabilised on the injection in hospital. Recommended dosage regimes for all indications:

A. Patients without previous exposure to a depot fluphenazine formulation:

Initially 0.5ml i.e. 12.5mg (0.25 ml i.e. 6.25mg for patients over 60) by deep intramuscular injection into the gluteal region.

The onset of action generally appears between 24 and 72 hours after injection and the effects of the drug on psychotic symptoms become significant within 48 to 96 hours. Subsequent injections and the dosage interval are determined

in accordance with the patient's response. When administered as maintenance therapy, a single injection may be effective in controlling schizophrenic symptoms for up to four weeks or longer.

It is desirable to maintain as much flexibility in the dose as possible to achieve the best therapeutic response with the least side-effects; most patients are successfully maintained within the dose range 0.5ml (12.5mg) to 4.0ml (100mg) given at a dose interval of 2 to 5 weeks.

Patients previously maintained on oral fluphenazine:
It is not possible to predict the equivalent dose of depot formulation in view of the wide variability of individual response.

B. Patients previously maintained on depot fluphenazine:

Patients who have suffered a relapse following cessation of depot fluphenazine therapy may be restarted on the same dose, although the frequency of injections may need to be increased in the early weeks of treatment until satisfactory control is obtained.

Elderly:
Elderly patients may be particularly susceptible to extrapyramidal reactions, sedative and hypotensive effects. In order to avoid this, a reduced maintenance dosage may be required and a smaller initial dose (see above).

Children:
Not recommended for children.

* Where a smaller volume of injection is desirable, patients may be transferred directly to the equivalent dose of Modecate Concentrate injection on the basis that 1ml Modecate Concentrate injection is equivalent to 4ml Modecate injection.

Note

The dosage should not be increased without close supervision and it should be noted that there is a variability in individual response.

The response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

Route of administration: Intramuscular.

4.3 Contraindications

The product is contraindicated in the following cases:

Comatose states
Marked cerebral atherosclerosis
Phaeochromocytoma
Renal failure
Liver failure
Severe cardiac insufficiency
Severely depressed states

Existing blood dyscrasias

Hypersensitivity to Fluphenazine Decanoate or to any of the excipients

Because of the content of benzyl alcohol Modecate injection must not be given to newborns or premature neonates.

4.4 Special warnings and precautions for use

Caution should be exercised with the following:

Liver disease
Renal impairment
Cardiac arrhythmias, cardiac disease
Thyrotoxicosis
Severe respiratory disease
Epilepsy, conditions predisposing to epilepsy (e.g. alcohol withdrawal or brain damage)
Parkinson's disease
Patients who have shown hypersensitivity to other phenothiazines
Personal or family history of narrow angle glaucoma
In very hot weather
The elderly, particularly 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 preventative 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.

Modecate contains benzyl alcohol as a preservative and must not be given to premature babies or neonates. The administration of medicines containing benzyl alcohol as a preservative may cause toxic reactions and anaphylactoid reactions in children up to 3 years old.

The administration of medications containing benzyl alcohol to newborns or premature neonates has been associated with fatal 'Gasping Syndrome' (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardio-vascular collapse). As benzyl alcohol may cross the placenta, solution for injection should be used with caution in pregnancy.

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 central nervous system depression produced by drugs such as alcohol, general anaesthetics, hypnotics, sedatives or strong analgesics.
2. Antagonise the action of adrenaline and other sympathomimetic agents 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 anti-convulsants; metabolism of tricyclic antidepressants; the control of diabetes.
4. Increase the effect of anticoagulants and antidepressants.
5. Interact with lithium.

Anticholinergic effects may be enhanced by anti-parkinsonian or other anticholinergic drugs.

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 adrenolytic 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 amfetamine/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 Fertility, pregnancy and lactation

Use in pregnancy: The safety for the use of this drug during pregnancy has not been established; therefore, the possible hazards should be weighed against the potential benefits when administering this drug to pregnant patients.

Neonates exposed to antipsychotics (including Modecate) 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.

Nursing mothers: Breast feeding is not recommended during treatment with depot fluphenazines, owing to the possibility that fluphenazine may be excreted in the breast milk.

4.7 Effects on ability to drive and use machines

The use of this drug may impair the mental and physical abilities required for driving a car or operating heavy machinery.

4.8 Undesirable effects

Side Effects: Acute dystonic reactions occur infrequently, as a rule within the first 24-48 hours, although delayed reactions may occur. In susceptible individuals they may occur after only small doses. These may include such dramatic manifestations as oculogyric crises and opisthotonos. They are 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 often decrease with subsequent injection. These reactions may be reduced by using smaller doses more frequently, or by the concomitant use of anti-parkinsonian drugs such as trihexyphenidyl, benzatropine or procyclidine. Anti-parkinsonian drugs should not be prescribed routinely, because of the possible risks of aggravating anti-cholinergic side effects or precipitating toxic confusional states, or of impairing therapeutic efficacy.

With careful monitoring of the dose the number of patients requiring anti-parkinsonian drugs can be minimised.

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible.

The syndrome is characterised 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: anti-parkinsonian 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.

Other Undesirable Effects: As with other phenothiazines, drowsiness, lethargy, blurred vision, dryness of the mouth, constipation, urinary hesitancy or incontinence, mild hypotension, impairment of judgement and mental skills, and epileptiform attacks are occasionally seen.

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

Blood dyscrasias have rarely been reported with phenothiazine derivatives. Blood counts should be performed if the patient develops signs of persistent infection. Transient leucopenia and thrombocytopenia have been reported. Antinuclear antibodies and SLE have been reported very rarely.

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

A transient rise in serum cholesterol has been reported rarely in patients on oral fluphenazine.

Abnormal skin pigmentation and lens opacities have sometimes been seen following long-term administration 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 treated with moderate to high dosage; they 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. Elderly or hypothyroid patients may be particularly susceptible to hypothermia. The hazard of hyperpyrexia may be increased by especially hot or humid weather, or by drugs such as anti-parkinsonian agents, which impair sweating.

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy. The syndrome is characterised by hyperthermia, together with some or all of the following: muscular rigidity, autonomic instability (labile blood pressure, tachycardia, diaphoresis), akinesia, and altered consciousness, sometimes progressing to stupor or coma. Leucocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur. Neuroleptic therapy should be discontinued immediately and vigorous symptomatic treatment implemented since the syndrome is potentially fatal.

Hormonal effects 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 been observed.

Oedema has been reported with phenothiazine medication.

Pregnancy, puerperium and perinatal conditions; drug withdrawal syndrome neonatal (see section 4.6) – Frequency not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Overdosage should be treated symptomatically and supportively, extrapyramidal reactions will respond to oral or parenteral anti-parkinsonian drugs such as procyclidine or benzatropine. In cases of severe hypotension, all procedures for the management of circulatory shock should be instituted, e.g. vasoconstrictors and/or intravenous fluids. However, only the vasoconstrictors metaraminol or noradrenaline should be used, as adrenaline may further lower the blood pressure through interaction with the phenothiazine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Phenothiazines with piperazine structure, ATC code: N05AB02

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

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

5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Sesame oil

6.2 Incompatibilities

None

6.3 Shelf life

18 months

The in use shelf life for the 10ml vial is 28 days.

6.4 Special precautions for storage

Store below 25ºC.

Do not refrigerate or freeze.

Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type I colourless glass ampoule containing 0.5, 1 and 2ml with an OPC (one point cut) break system.

Type I Glass cartridge syringes with Helvoet Pharma rubber plungers and stoppers containing 1 and 2ml.

Type I Glass vials with pharma-gummi rubber stoppers containing 10ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited

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