Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Modecate Concentrate 100 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 100mg Fluphenazine Decanoate.
Each 0.5ml of solution contains 50mg Fluphenazine Decanoate.

Excipients: contains 15mg benzyl alcohol per ml and sesame oil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)
A clear yellow, oily solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the long-term management of psychotic disorders such as chronic schizophrenia, the disturbed elderly, severe anxiety tension states and personality disorders.

Modecate is not intended for use in nonpsychotic disorders or for short-term therapy (< 3 months).

Modecate has not been shown to be effective in the management of behavioural complications in patients with mental retardation.

4.2 Posology and method of administration

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

The usual initial dose is 12.5mg by deep intramuscular injection into the gluteal region (reduced to 6.25 mg in patients over 60). Subsequent dosage is usually 25mg every two to four weeks, with a range of 12.5 to 100mg, depending on the patient's response. In those with no previous therapy with a depot fluphenazine formulation, treatment can be initiated by the oral route or using a quick-acting agent before transferring to this form.

Dosage should not exceed 100 mg. If doses greater than 50 mg are deemed necessary, the next dose and succeeding doses should be increased cautiously in increments of 12.5 mg

Severely agitated patients may be treated initially with a rapid-acting phenothiazine compound such as fluphenazine hydrochloride injection. When acute symptoms subsided, 25 mg (1mL) of modecate may be administered; subsequent dosage is adjusted as necessary.

Elderly:
Elderly patients may be particularly susceptible to extrapyramidal reactions. Therefore reduced maintenance dosage may be required and a smaller initial dose (see above).

Children:
Not recommended for children

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 If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

4.3 Contraindications

Comatose states
Suspected or established subcortical brain damage
Marked cerebral atherosclerosis
Phaeochromocytoma
Renal failure
Liver failure
Severe cardiac insufficiency
Severely depressed states
Hypersensitivity to any of the ingredients of the formulation
Patients receiving large doses of CNS depressants (e.g. alcohol, barbiturates, narcotics, hypnotics etc.)
Existing blood dyscrasias
Caution should be observed in patients with a history of sensitivity to other phenothiazines, as cross-sensitivity may occur.

4.4 Special warnings and precautions for use

Caution should be exercised in patients with the following conditions:

Liver disease
Cardiac arrhythmias, mitral insufficiency, risk factors for stroke or cardiovascular disease or family history of QT prolongation
Thyrotoxicosis
Severe respiratory disease
Parkinson's disease
Patients who have developed cholestatic jaundice, dermatoses or other allergic reactions to phenothiazine derivatives.
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 exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders (since grand mal convulsions have been known to occur in patients on therapy with fluphenazine).

Avoid concomitant antipsychotics.

Patients taking this medication should carry a treatment card indicating dosage received.

Patients undergoing surgery should be carefully monitored for possible hypotensive phenomena and the doses of anaesthetics or other CNS depressant used may need to be reduced (see sections 4.3 and 4.5).

During the first months of treatment routine blood count and liver function tests are advisable as blood dyscrasia (including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia) and liver dysfunction may occur. Furthermore, if any soreness of the mouth, gums, or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates bone marrow depression, therapy should be discontinued and other appropriate measures instituted immediately.

This product contains 15 mg of benzyl alcohol per ml. Benzyl alcohol must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to three years old.

This product contains sesame oil which may rarely cause severe allergic reactions.

Potentiation of the effects of alcohol may occur with the use of this drug (see section 4.3).

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 Modecate, and preventive measures undertaken.

As with any phenothiazine, the physician should be alert to the possible development of pneumonia in patients under prolonged treatment with fluphenazine decanoate.

Patients at Risk
Patients with a known hypersensitivity to phenothiazines should be carefully monitored if fluphenazine is given. Patients with symptoms such as depression, confusion, or weight loss, should be carefully evaluated to exclude a diagnosis of atypical mood disorders before initiating treatment with fluphenazine. When the pharmacologic effects and an appropriate dosage are apparent, an equivalent dose of Modecate Injection may be administered. Subsequent dosage adjustments are made in accordance with the response of the patient (see section 4.2).

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.

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

Abrupt Withdrawal

In general, phenothiazines do not produce psychic dependence; however, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported within 2 to 4 days following abrupt cessation of high-dose therapy and have been reported to subside in 1 to 2 weeks. Reports suggest that these symptoms can be reduced by gradual reduction of the dosage or by continuing concomitant anti-Parkinson agents for several weeks after the phenothiazine is withdrawn(see sections 4.5 and 4.8).

Neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically (see sections 4.4 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Antihypertensives: The antihypertensive action of guanethidine, clonidine and possibly other adrenergic-blocking antihypertensive agents may be blocked. Clonidine may decrease the antipsychotic activity of phenothiazines.

Medicines that prolong the QT Interval: Medicines that can prolong the QT interval should be avoided, as should any medicine that can cause electrolyte imbalance or an increase in the concentration of fluphenazine in the blood. (See section 4.4)

P450 Enzyme substrates or inhibitors: Fluphenazine is metabolized by P450 2D6 and is itself an inhibitor of this drug-metabolizing 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 cardiac

toxicity, anticholinergic side effects, or orthostatic hypotension.

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.

CNS Depressants/Alcohol/Analgesics: The patient's response to alcohol and other CNS depressants, such as hypnotics, sedatives or strong analgesics, may be exaggerated while taking Modecate. Combined use with narcotic analgesics may cause hypotension as well as CNS or respiratory depression (see sections 4.3 and 4.4).

Tricyclic Antidepressants: Phenothiazines impair the metabolism of tricyclic antidepressants. Serum concentrations of both the tricyclic and phenothiazine are increased. Sedative and antimuscarinic effects may be potentiated or prolonged. Tricyclics may increase potential for arrhythmia.

Lithium: Neurotoxicity has been reported when lithium is used concomitantly with fluphenazine

ACE inhibitors/Thiazide Diuretics: Hypotension may result via additive or synergistic pharmacological activity.

Beta Blockers: Plasma levels of both drugs may be increased. Dosage reduction of both drugs is recommended.

Metrizamide: Phenothiazines may predispose patients to metrizamide-induced seizures. Discontinue fluphenazine decanoate for 48 hours prior to and for at least 24 hours after myelography.

Epinephrine and other sympathomimetics: Phenothiazines may antagonize the action of adrenaline and other sympathomimetics and may cause severe hypotension.

Levodopa: Phenothiazines may impair the anti-Parkinson effect of L-Dopa.

Anticholinergics/Antimuscarinics: Cholinergic blockade may be exaggerated when Modecate is administered with anticholinergic agents, especially in older patients. Antimuscarinic effects may be potentiated or prolonged. Close supervision and careful dosage adjustment are required when Modecate is used with other anticholinergic or antimuscarinic drugs.

Anticonvulsants: Anticonvulsant action may be impaired by Modecate

Anticoagulants: Phenothiazines may alter the effects of anticoagulants.

Antidiabetics: Phenothiazines have been associated rarely with loss of blood glucose control in patients with diabetes.

Monoamine oxidase inhibitors: Modecate may increase the effect of monoamine oxidase inhibitors.

Quinidine and other anti-arrythmics: the cardiac- depressant effects may be enhanced by phenothiazines.

Corticosteriods, digoxin and neuromuscular blocking agents: the absorption of these drugs may be enhanced by phenothiazines.

4.6 Fertility, pregnancy and lactation

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.
The safety of 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. The lowest possible dose should be administered for the shortest duration.

Breast-feeding
Nursing Mothers: Breast feeding is not recommended during treatment with depot fluphenazines, owing to the possibility that fluphenazine is excreted in the milk of nursing mothers.

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

The adverse events reported most frequently with phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Most often these extrapyramidal symptoms are reversible; however, they may be persistent. With any given phenothiazine derivative, the incidence and severity of such events depend more on individual patient sensitivity than on other factors, but dosage level and patient age are also determinants.

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 injections. These reactions may be reduced by using smaller doses more frequently, or by the concomitant use of anti-Parkinsonian drugs such as benzhexol, benztropine 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

Tardive dyskinesia, a syndrome characterised by involuntary dyskinetic movements, may develop in patients on antipsychotic therapy and occasionally even in those who have discontinued or never received such treatment. Those at particular risk include the elderly, females and patients on high dosage or prolonged therapy, i.e. with a high total cumulative dose. Nonetheless, the syndrome can develop without such factors being involved. The syndrome may be irreversible, or only slowly reversed, if neuroleptic treatment is withdrawn. Fine, vermicular movements of the tongue are reported to be an early sign and if the medication is discontinued the syndrome may not progress.

In an attempt to minimise the possibility of the development of such a syndrome, major tranquilliser therapy should be reserved for patients for whom it is essential, the dosage used should be the lowest commensurate with optimal benefit, and duration of treatment should not extend beyond that necessary for the patient.

There is no known treatment for tardive dyskinesia. The antipsychotic drug may mask it, as may anticholinergic agents.

Neuroleptic Malignant Syndrome

The potentially fatal syndrome may occur with use of any neuroleptic agent. Symptoms include clouding of consciousness, rigidity and other extrapyramidal effects, and automonic dysfunction (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias), most importantly hyperpyrexia. Leukocytosis, fever, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS. Treatment involves the immediate cessation of neuroleptic therapy, intensive symptomatic management and monitoring as appropriate and treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy

should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Others

Blood dyscrasias, including agranulocytosis, have been reported with phenothiazine derivatives, which may increase the potential susceptibility to infection. Blood counts should be performed if the patient develops signs of persistent infection. Transient leucopenia and thrombocytopenia have been reported (see section 4.4) Antinuclear antibodies and SLE have been reported.

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

Fever, vomiting, systemic lupus erythematosus like syndrome, altered ECG tracings, liver or kidney damage, development of irreversible dyskinesia abnormal skin pigmentation and lens opacities, including cataracts, have sometimes been seen following long-term administration of high doses of phenothiazines (see section 4.4). There have been reports of retinopathy and pigmentary retinal deposits in patients receiving fluphenazine at high doses or for prolonged periods.

Hypotension has rarely presented a problem with fluphenazine. However, 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. If severe hypotension should occur, supportive measures, including the use of intravenous vasopressor drugs, should be instituted immediately. Levarterenol bitartrate injection is the most suitable drug for this purpose; epinephrine should NOT be used, since phenothiazine derivatives have been found to reverse its action, resulting in a further lowering of blood pressure.

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 are reversible on reducing the dose. In a very small number of cases, 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. Cardiac arrest and torsades de pointes have been reported with anti-psychotic agents.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized, placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Fluphenazine decanoate should be used with caution in patients with risk factors for stroke.

Phenothiazines may impair body temperature regulation. Cases of severe hypothermia or hyperpyrexia have been reported in association with moderate or high dosage of phenothiazines.

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.

Hormonal effects of fluphenazines include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea. Sexual function may be impaired.

Oedema has been reported with phenothiazine medication.
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown.

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

The list below is presented by system organ class, MedDRA preferred term, and frequency using the following

frequency categories: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), and not known (cannot be estimated from the available data).

MedDRA SOC	MedDRA Preferred Term	Frequency
Infections and infestations	**Upper respiratory tract infection**	Not known
Blood and lymphatic system disorders	**Pancytopenia**	Not known
	Agranulocytosis	Not known
	Thrombocytopenic purpura	Not known
	Purpura non-thrombocytopenic	Not known
	Leukopenia	Not known
	Eosinophilia	Not known
Immune system disorders	**Anaphylactic reaction**	Not known
Investigations	**Pregnancy test false positive**	Not known
Metabolism and nutrition disorders	**Inappropriate antidiuretic hormone secretion**	Not known
	Hyponatraemia	Not known
	Anorexia	Not known
	Weight fluctuation	Not known
Psychiatric disorders	**Restlessness**	Not known
	Agitation	Not known
	Abnormal dreams	Not known
Nervous system disorders	**Neuroleptic malignant syndrome**	Not known
	Cerebrovascular accident	Not known
	Brain oedema	Not known
	Tardive dyskinesia	Not known
	Extrapyramidal disorder	Not known
	Parkinsonism	Not known
	Dystonia	Not known
	Dyskinesia	Not known
	Akathisia	Not known
	Oculogyration	Not known
	Opisthotonos	Not known
	Hyperreflexia	Not known
	Choreoathetosis	Not known
	Somnolence	Not known
	Lethargy	Not known
	Electroencephalogram abnormal	Not known
	Cerebrospinal fluid protein abnormal	Not known
	Headache	Not known
Eye disorders	**Glaucoma**	Not known
	Vision blurred	Not known
	Lenticular opacities	Not known
	Corneal opacity	Not known
Cardiac disorders	**Cardiac arrest**	Not known
	Torsade de pointes	Not known
	Ventricular arrhythmia	Not known
	Ventricular fibrillation	Not known
	Ventricular tachycardia	Not known

	Electrocardiogram QT prolonged	Not known
	Electrocardiogram abnormal	Not known
Vascular disorders	**Hypertension**	Not known
	Blood pressure fluctuation	Not known
	Hypotension	Not known
	Thromboembolic disorders	Not known
Respiratory, thoracic and mediastinal disorders	**Asthma**	Not known
	Laryngeal oedema	Not known
	Nasal congestion	Not known
Gastrointestinal disorders	**Ileus paralytic**	Not known
	Faecaloma	Not known
	Dry mouth	Not known
	Constipation	Not known
	Salivary hypersecretion	Not known
	Oral pain	Not known
	Gingival pain	Not known
	Pharyngolaryngeal pain	Not known
	Nausea	Not known
	Vomiting	Not known
Hepatobiliary disorders	**Hepatitis**	Not known
	Jaundice cholestatic	Not known
	Jaundice	Not known
	Liver function test abnormal	Not known
	Hepatic function abnormal	Not known
Skin and subcutaneous tissue disorders	**Dermatitis exfoliative**	Not known
	Angioneurotic oedema	Not known
	Photosensitivity reaction	Not known
	Urticaria	Not known
	Seborrhoea	Not known
	Erythema	Not known
	Eczema	Not known
	Hyperhidrosis	Not known
	Pruritus	Not known
	Pigmentation disorder	Not known
Musculoskeletal, connective tissue and bone disorders	**Systemic lupus erythematosus**	Not known
	Blood creatine phosphokinase increased	Not known
Renal and urinary disorders	**Renal failure acute**	Not known
	Neurogenic bladder	Not known
	Polyuria	Not known
Reproductive system and breast disorders	**Gynaecomastia**	Not known

	Menstruation irregular	Not known
	Lactation disorder	Not known
	Erectile dysfunction	Not known
	Libido disorder	Not known
General disorders and administration site condition	**Sudden death**	Not known
	Oedema peripheral	Not known
	Pyrexia	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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie

4.9 Overdose

In general, the symptoms of overdose are extensions of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) sedation. CNS depression may progress to coma with areflexia. Restlessness, confusion and excitement may occur with early or mild intoxication. The drug should be withdrawn and the symptoms of overdose treated supportively.
If severe hypotension should occur, supportive measures, including the use of intravenous vasopressor except for adrenaline are the most suitable drugs for this purpose. In case of severe extrapyramidal reactions, anti-Parkinson medication should be administered, and should be continued for several weeks. Anti-Parkinson medication should be withdrawn gradually to avoid the emergence of rebound extrapyramidal symptoms. Limited experience indicates that phenothiazines are not dialyzable. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis are ineffective in phenothiazine poisoning.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

A phenothiazone derivative, widely distributed, metabolised in the liver and excreted via kidney and entero-biliary tract with a T½ of 2.5 weeks to 16 weeks.

5.3 Preclinical safety data

No further information is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Sesame oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years.
Once opened, use immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.
Keep ampoules in the outer carton to protect from light.

6.5 Nature and contents of container

0.5ml Ampoules:
10 x Type I glass ampoules of 0.5ml. The outer carton contains two packs. Each pack contains 5 ampoules, each marked with a green band and red band, enclosed in a cardboard carton with a leaflet.

1.0ml Ampoules:
5 x Type I clear glass ampoules of 1.0ml. Each pack contains 5 ampoules, marked with red band and a blue band, enclosed in a cardboard carton with a leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused contents.

Refrigeration will cause precipitation of triglycerides from the sesame oil. If precipitation does occur, warming the product to 37°C will dissolve the precipitate without harming the active ingredient.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals uc
Plaza 254, Blanchardstown Corporate Park 2, Ballycoolin
Dublin 15, D15 T867
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0002/031/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 25 January 2009

10 DATE OF REVISION OF THE TEXT

November 2017