

SUMMARY OF PRODUCT CHARACTERISTICS (CORE SPC)

1. NAME OF MEDICINAL PRODUCT

Deanxit® coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Flupentixol 0.5 mg (as dihydrochloride).

Melitracen 10 mg (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets.

Round, biconvex, cyclamen, sugar-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety – Depression – Asthenia.

Neurasthenia, Psychogenic depression. Depressive neuroses. Masked depression. Psychosomatic affections accompanied by anxiety and apathy. Menopausal depressions. Dysphoria and depression in alcoholics and drug-addicts.

4.2 Posology and method of administration

4.2.1 Posology

Adults

Usually 2 tablets daily: morning and noon.

In severe cases the morning dose may be increased to 2 tablets.

The maximum dose is 4 tablets daily.

Elderly patients (> 65 years)

1 tablet in the morning.

In severe cases 1 tablet in the morning and 1 at noon.

Maintenance dose: Usually 1 tablet in the morning.

In cases of insomnia or severe restlessness additional treatment with a sedative in the acute phase is recommended.

Children and adolescents (<18 years)

Deanxit is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Reduced renal function

Deanxit can be given in the recommended doses.

Reduced liver function

Deanxit can be given in the recommended doses.

Method of administration

The tablets are swallowed with water.

4.3 Contra-indications

Hypersensitivity to flupentixol and melitracen or to any of the excipients.

Circulatory collapse, depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), coma, blood disorders, phaeochromocytoma.

Recent myocardial infarction. Any degree of atrioventricular block or disorders of cardiac rhythm and coronary artery insufficiency.

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5).

Simultaneous administration of melitracen and MAO inhibitors may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

As with other tricyclic antidepressants, melitracen should not be given to patients receiving monoamine oxidase inhibitors (MAOIs). Treatment with Deanxit may be instituted 14 days after discontinuation of non-selective MAOIs and minimum one day after discontinuation of moclobemide and selegiline. Treatment with MAOIs may be introduced 14 days after discontinuation of Deanxit.

4.4 Special warnings and precautions for use

Deanxit should not be administered together with MAOIs (see section 4.3 and section 4.5).

Deanxit should be used with caution in patients with organic brain syndrome, convulsion, urinary retention, hyperthyroidism and advanced hepatic or cardiovascular disease.

Not recommended for excitable or overactive patients since its activating effect may lead to exaggeration of these characteristics. If previously the patient has been treated with tranquilizers or neuroleptics with sedative effect, these should be withdrawn gradually.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs, either spontaneously or following treatment. Patients being treated with antidepressants should be monitored carefully especially at the beginning of treatment for clinical worsening and/or the emergence of suicidality (suicidal ideation and behaviour). This precaution should also be observed when treating other psychiatric disorders because of the possibility of co-morbidity with major depressive disorder.

Potentially suicidal patients should not have access to large quantities of drugs.

As described for other psychotropics Deanxit may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue Deanxit several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated.

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 Deanxit and preventive undertaken.

Use in children and adolescents under the age of 18

Tricyclic antidepressants (TCA) should not be used in the treatment of depression in children and adolescents under the age of 18 years. Studies in depression in this age group did not show a beneficial effect for the class of TCAs. Suicide related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. In addition, TCAs are associated with a risk of cardiovascular adverse events in all age groups.

Excipients

The tablets contain lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose or fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not receive this medicine.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Deanxit is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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.

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

4.5 Interactions with other medicinal products and other forms of interactions

Contraindicated combinations

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) - risk of "serotonin syndrome" (see section 4.3).

Inadvisable combinations

Sympathomimetic agents: Melitracen may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

Adrenergic neurone blockers: Deanxit may counteract the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Anticholinergic agents Tricyclic antidepressants may potentiate the effects of these drugs on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc.

Combinations requiring precautions for use

CNS depressants: Deanxit may enhance the effects of alcohol, barbiturates and other CNS depressants.

Concomitant use of neuroleptics (flupentixol) and lithium increases the risk of neurotoxicity. Deanxit may reduce the effect of levodopa and increase the risk of cardiac side effects.

4.6 Pregnancy and lactation

Pregnancy

Deanxit should not be administered during pregnancy unless the expected benefit to the patient outweighs the theoretical risk to the foetus. Due to the risk of neonatal withdrawal symptoms it is recommended that Deanxit treatment is stopped about 14 days before delivery by tapering off the dosage.

Neonates exposed to antipsychotics (including Deanxit) 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.

Animal-reproduction studies have not given evidence of an increased incidence of foetal damage or other deleterious effects on the reproduction process.

Lactation

As flupentixol is found in breast milk in low concentrations it is not likely to affect the infant when therapeutic doses are used. The dose ingested by the infant is less than 0.5% of the weight related maternal dose (in mg/kg).

It is not known whether melitracen is excreted in breast milk. However, another tricyclic antidepressant, amitriptyline, is found in breast milk in low concentrations and it is not likely to affect the infant when therapeutic doses are used. The dose ingested by the infant is about 2% of the weight related maternal daily dose (in mg/kg). As melitracen has the same lipophilic properties as amitriptyline, it is assumed that it occurs in breast milk in similar concentrations.

Breast-feeding can be continued during Deanxit therapy if considered of clinical importance but observation of the infant is recommended, particularly in the first 4 weeks after giving birth.

4.7 Effects on ability to drive and use machines

Deanxit is a non-sedating drug in the recommended dosage range.

However, patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery.

4.8 Undesirable effects

4.8.1 Clinical trials

There are few and mild adverse effects. Insomnia (in 6%) is the most frequent adverse effect.

In the listing below the following convention is used:

MedDRA system organ class / preferred term

Very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000).

The following frequencies have been reported in clinical trials:

MedDRA SOC	Frequency	Preferred Term
Psychiatric disorders	Common (>1/100, <1/10)	Insomnia, restlessness, agitation
	Not known	Suicidal ideation, suicidal behaviour ¹
Nervous system disorders	Common (>1/100, <1/10)	Dizziness, tremor
Gastrointestinal disorders	Common (>1/100, <1/10)	Dry mouth, constipation
Eye disorder	Common (>1/100, <1/10)	Accommodation disorder
General disorders and administration site conditions	Common (>1/100, <1/10)	Fatigue
Pregnancy, puerperium and perinatal conditions.	Not known	Drug withdrawal syndrome neonatal (see 4.6)

Post marketing

Isolated cases of cholestatic hepatitis have been reported.

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

4.9 Overdose effects

In cases of overdosage the symptoms of intoxication by melitracen, especially of anticholinergic nature, dominate. More rarely extrapyramidal symptoms due to flupentixol occur.

Symptoms

Somnolence or excitation, agitation, hallucinations. Anticholinergic effects: Mydriasis, tachycardia, urinary retention, mucosal dryness, intestinal hypomotility. Convulsions. Pyrexia. Depressed level of consciousness, coma, respiratory depression. Cardiac symptoms: Arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation); cardiac failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia.

Treatment

Admission to hospital (intensive care unit). Treatment is symptomatic and supportive. Gastric aspiration and lavage even in a late stage after oral ingestion and treatment with

¹ Cases of suicidal ideation and suicidal behaviours have been reported during flupentixol therapy or early after treatment discontinuation (see section 4.4).

activated charcoal. Measures to support the respiratory and cardiovascular systems should be instituted. Continuous ECG-monitoring of cardiac function for 3-5 days. Epinephrine (adrenaline) should not be used as further lowering of blood pressure may result. Convulsions may be treated with diazepam and extrapyramidal symptoms with biperiden.

Adults have survived consumption of up to 100 tablets (1000 mg melitracen and 50 mg flupentixol) and an almost 3-year old child 27 tablets (270 mg melitracen and 13,5 mg flupentixol).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Antidepressants – Tricyclic antidepressant (melitracen) and neuroleptic of the thioxanthene group (flupentixol).

ATC-code: N 06 CA 02

Deanxit consists of two well known and well proven compounds:

Flupentixol is a neuroleptic of the thioxanthene group with anxiolytic and antidepressant properties when given in small doses.

Melitracen is a tricyclic antidepressant with activating properties in low doses. It has similar pharmacological properties as amitriptyline but is less sedative.

In combination the compounds render a preparation with antidepressant, anxiolytic and activating properties.

5.2 Pharmacokinetic properties

Flupentixol

Flupentixol is a mixture of two geometric isomers, the active cis(Z)-flupentixol and trans(E)-flupentixol, approximately in the ratio of 1:1.

The following data concerns the active cis(Z)-isomer.

Absorption

Oral administration results in maximum serum levels in about 4-5 hours. Oral bioavailability is about 40%.

Distribution

The apparent volume of distribution (V_d)_β is about 14.1 l/kg.

The plasma protein binding is about 99%.

Biotransformation

The metabolism of cis(Z)-flupentixol proceeds along three main routes – sulfoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid

of psychopharmacological activity. Flupentixol dominates over metabolites in brain and other tissues.

Elimination

The elimination half-life ($T_{1/2\beta}$) is about 35 hours and the mean systemic clearance (Cl_s) is about 0.29 l/min.

Flupentixol is excreted mainly with faeces, but also to some degree with the urine.

When tritium labelled flupentixol was administered to man the excretion pattern shows the excretion via faeces to be about 4 times the urinary excretion.

In nursing mothers flupentixol is excreted in small amounts with the breast milk. The ratio milk conc./serum conc. in women is on an average 1.3.

Linearity

The kinetics is linear. Steady state plasma levels are achieved in about 7 days. The mean minimum steady state level corresponding to 5 mg flupentixol orally once-a-day was about 1.7 ng/ml (3.9 nmol/l).

Elderly patients

Pharmacokinetic investigations have not been done in elderly patients. However, for the related thioxanthene drug, zuclopenthixol, the pharmacokinetic parameters are widely independent of the age of the patient.

Reduced hepatic function

No data available.

Reduced renal function

Based on the above characteristics for elimination it is reasonable to assume that reduced kidney function is likely not to have much influence on the serum levels of parent drug.

Melitracen

Absorption

Oral administration results in maximum serum levels in about 4 hours. Oral bioavailability is not known.

Distribution

The apparent volume of distribution (V_d) $_{\beta}$ is not known. The plasma protein binding in rats is about 89%.

Biotransformation

The metabolism of melitracen proceeds mainly by demethylation and hydroxylation. The main active metabolite is the secondary amine, litracen.

Elimination

The elimination half-life ($T_{1/2\beta}$) is about 19 hours (range 12-24 hours) in man. The systemic clearance (Cl_s) is not known.

In rats melitracen is excreted mainly with faeces, but also to some degree with the urine. The excretion pattern showed the excretion via faeces to be about 2½ times the urinary excretion.

It is not known whether melitracen is excreted with breast milk.

Elderly patients

No data available.

Reduced hepatic function

No data available.

Reduced renal function

No data available.

5.3 Preclinical safety data

Acute toxicity

Flupentixol has low acute toxicity, but the acute toxicity of tricyclic antidepressants including melitracen is high.

Chronic toxicity

In chronic toxicity studies there were no findings of concern for the therapeutic use of flupentixol or melitracen.

Reproduction toxicity

Based on data from reproduction toxicity studies there is no reason to have special concern for the use of flupentixol or melitracen in women of child-bearing potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Lactose monohydrate, potato starch, talc, gelatin, magnesium stearate.

Coating: Gelatin, sucrose, sucrose powder.

Deanxit colour (erythrosine E 127 and indigotine E 132).

Polishing wax: Capol 1295® (a mixture of Beeswax, white wax and carnauba wax).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Each pack has an expiry date.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

50 and 100 in blister packs.

6.6 Instructions for use / handling

None.

7. MARKETING AUTHORISATION HOLDER

C.G. Papaloisou Ltd, 35 Kilkis Ave., 2234 Latsia, Cyprus

7.1 Manufacturer

H. Lundbeck A/S
Ottiliavej 9
DK-2500 Copenhagen
Denmark.

8. MARKETING AUTHORISATION NUMBER

4658

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2 January 1998

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2 April 2012