Package Insert

DEANXIT FILM-COATED TABLET

1. NAME OF THE MEDICINAL PRODUCT

Deanxit film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Flupentixol 0.5 mg (as 0.584mg flupentixol dihydrochloride)
Melitracen 10 mg (as 11.25mg melitracen hydrochloride)

Excipients with known effect:
Lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Round, biconvex, cyclamen, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety − Depression − Asthenia.

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

Adults
Usually 2 tablets daily: morning and noon.
In severe cases the morning dose may be increased to 2 tablets.

Older people (> 65 years)
1 tablet in the morning.

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.

Paediatric population
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
No clinical data of exposure in patients with reduced renal function are available.

Reduced liver function
No clinical data of exposure in patients with reduced liver function are available.

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.

Untreated narrow angle glaucoma.

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 nonselective MAOIs. Treatment with MAOIs may be introduced 14 days after discontinuation of Deanxit.

Not recommended for excitable or overactive patients since its activating effect may lead to exaggeration of these characteristics.

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 tranquillizers or neuroleptics with sedative effect, these should be withdrawn gradually.

Depression is associated with an increased risk of suicide. This risk may persist until significant remission occurs, either spontaneously and/ or following treatment. Patients with depression should be monitored carefully especially at the beginning of their illness for mentally worsening and possible accompanying suicidal behaviour.
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.

Use in children and adolescents under the age of 18
Deanxit is not recommended for use in children and adolescents due to lack of data on efficacy and safety. Treatment with Deanxit is associated with a risk of cardiovascular adverse events in all age groups.

Excipients
The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interactions

Contraindicated combinations
Simultaneous administration of MAO-inhibitors may cause hypertensive crises.

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 Fertility, 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 studies have shown reproductive toxicity (see section 5.3)

Breast-feeding

Flupentixol is found in breast milk in low concentrations. It is not known whether melitracen is excreted in breast milk. It is assumed that it will be found in breast milk in low concentrations. If the use of Deanxit is considered essential, nursing mothers should be advised to stop breast-feeding.

Fertility
In humans, adverse events have been reported that may have a negative impact on female and/ or male sexual function and fertility. If clinical significant hyperprolactinaemia, galactorrhoea, amenorrhoea or sexual dysfunctions occur, a dose reduction (if possible) or discontinuation should be considered.
The effect is reversible on discontinuation.

In preclinical fertility studies in rats, where flupentixol and melitracen were administered separately slight effects on fertility were noted. Flupentixol slightly affected the pregnancy rate of female rats, whereas melitracen slightly repressed fertility and fecundity of male rats. Effects were seen at doses well in excess of these applied during clinical use.

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

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	Insomnia, restlessness, agitation.
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	Common (>1/100, <1/10)	Fatigue

site conditions		

Post marketing
Isolated cases of cholestatic hepatitis have been reported.

4.9 Overdose

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

Symptoms
Somnolence or irritability, 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 arrhythmia, torsade de pointes, ventricular fibrillation); cardiac failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalaemia.

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 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 disorder with biperiden.

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.

Absorption
Oral administration results in maximum serum levels in about 12 hours.
Oral bioavailability is about 40%.

Distribution
The apparent volume of distribution $(V_d)_\beta$ is about 14.1 l/kg.
The plasma protein binding is about 99%.

Biotransformation
The metabolism of flupentixol proceeds along three main routes – sulphoxidation, 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 ($T_{½\,\beta}$) is about 61 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).

Older people
Pharmacokinetic investigations have not been done in elderly patients.

Reduced hepatic function
No data available.

Melitracen
Absorption
Oral administration results in maximum serum levels in about 5 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 ($T_{½\,\beta}$) is about 62 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.

Older people
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
In preclinical fertility studies in rats, where flupentixol and melitracen were administered separately slight effects on fertility were noted. Flupentixol slightly affected the pregnancy rate of female rats, whereas melitracen slightly repressed fertility and fecundity of male rats. Effects were seen at doses well in excess of those applied during clinical use.

Combination of flupentixol and melitracen did not induce major malformations or affect pregnancy and embryofoetal development in rats or rabbits. In mice melitracen was associated with lower foetal body weight, but no major malformations were noted.

No effect on parturition or postnatal development of melitracen was noted in mice or rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Betadex
Lactose monohydrate,
Maize starch,
Hydroxypropylcellulose,
Microcrystalline cellulose,
Croscarmellose sodium
Talc,
Hydrogenated vegetable oil
Magnesium stearate.

Coating:
Polyvinyl alcohol part hydrolyzed,
Macrogol 3350
Talc,
Macrogol 6000

Colours:
Titanium dioxide E 171,
Erythrosine E127,
Indigotine E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Each pack has an expiry date.

6.4 Special precautions for storage

Store below 30° C. Protect from light.

6.5 Nature and contents of container

20, 30, 50, 60 and 100 in blister packs.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER / MANUFACTURER

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Ottiliavej 9
2500 Valby
Denmark

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