IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0019/015/001
Case No: 2014474

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pfizer Limited

Ramsgate Road, **Sandwich**, **Kent CT13 9NJ**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

SINEQUAN Capsules 75mg

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/01/2006** until **29/09/2007** .

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

SINEQUAN™ Capsules 75mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains doxepin hydrochloride equivalent to 75mg doxepin

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Sinequan 75mg capsule: Size no.2 Opaque, blue/yellow hard gelatin capsules having the monogram 'Pfizer' and the identifying code 'SQN 75' imprinted on the capsule shells and containing a white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of anxiety and for depression including reactive psychosomatic and endogenous types, or in anxiety/tension states associated with diagnostic procedures.

4.2 Posology and method of adminstration

Adults Only:

The optimum oral dose depends on the severity of the condition and the individual patient's response. The dose varies from 30-300mg daily. Doses up to 100mg daily may be given on a divided or once daily schedule. Should doses over 100mg daily be required, they should be administered in three divided doses daily. 100mg is the maximum dose recommended at any one time. This dose may be given at bedtime.

For the majority of patients with moderate or severe symptoms, it is recommended that treatment commences with an initial dose of 75mg daily. Many of these patients will respond satisfactorily at this dose level. For patients who do not, the dosage may be adjusted according to individual response. In more severely ill patients, it may be necessary to administer a dose of up to 300mg a day to obtain a clinical response.

In patients where insomnia is a troublesome symptom, it is recommended that the total daily dose be divided so that a higher proportion is given for the evening dose; similarly, if drowsiness is experienced as a side effect of treatment, Sinequan may be administered by this regimen, or the dosage may be reduced.

It is often possible, having once obtained a satisfactory therapeutic response, to reduce the dose for maintenance therapy.

The anti-anxiety effect is apparent before the antidepressant effect. The optimal antidepressant effect may not be evident for two to three weeks.

Children:

Use with great caution as the young are likely to show behavioural effects or postural hypotension. The use of Sinequan in children under 12 years is contraindicated. (See Section 4.4 Special Warnings and Special Precautions for Use)

Elderly:

In general, lower dosages are recommended. Where the presenting symptoms are mild in nature, it is advisable to initiate treatment at a dose of 10-50 mg daily. A satisfactory clinical response is obtained in many of these patients at a daily dose of 30-50mg. The dosage should be adjusted carefully according to the individual patient's response.

Use with great caution as the elderly are likely to show toxic effects, especially agitation, confusion or postural hypotension.

Use in hepatic impairment:

Dosage reduction may be required in patients with hepatic impairment. (See Special warnings and special precautions for use).

Use in renal impairment: (See Special warnings and special precautions for use).

Treatment with Sinequan should not be stopped abruptly, but reduced gradually through downtitration.

4.3 Contraindications

Use in patients who have shown hypersensitivity to doxepin, similar antidepressants or other constituents of the product.

Use in patients in the acute recovery phase of myocardial infarction.

Use in patients with cardiac arrhythmias, particularly heart block.

Use in patients with severe liver dysfunction.

Use in patients currently receiving, or within two weeks of cessation of therapy with monoamine oxidase (MAO) inhibitors.

Use in children under 12 years of age, because safe conditions for its use have not been established.

Use during lactation in women breast-feeding infants. Doxepin and its active metabolite desmethyldoxepin are excreted in breast milk. There has been a report of apnoea and drowsiness occurring in a nursing infant whose mother was taking doxepin.

Use in patients with glaucoma or a tendency to urinary retention. These disorders should be excluded, particularly in older patients.

4.4 Special warnings and precautions for use

The once-a-day dosage regimen of Sinequan in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Sinequan should only be used with great caution in patients with a history of epilepsy or recent convulsions, schizophrenia, hepatic insufficiency, hyperthryroidism, cardiovascular disorders or in conjunction with

electroconvulsive therapy. Exacerbation of schizophrenia or pre-existent agitation or mania may occur.

Patients receiving tricyclic antidepressant therapy should be kept under regular surveillance with particular attention to the possibility of effects on cerebral function or cardiac conduction disorders.

Since suicide is an inherent risk in any depressed patient until significant improvement has occurred, patients should be closely supervised during early therapy.

Doxepin should not be used in the treatment of children and adolescents uunder the age of 18 years. Studies in depression in this age group did not show a beneficial effect for tricyclic antidepressants. Studies with other classes of antidepressants (SSRIs and SNRIs) have showm a risk of suicidality, self-harm and hostility related to these compounds. This risk cannot be excluded with doxepin. In addition, doxepin is associated with a risk of cardiovascular adverse events in all age groups. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see also section 4.8 Undesirable effects and Section 4.9 Overdose).

If patients on tricyclic anti-depressants require surgery, the anaesthetist should be informed of medications in advance in view of the risk of cardiovascular complications.

Patients should be warned that drowsiness may occur with the use of this drug.

It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional doxepin overdosage. This is especially important in patients who may use alcohol excessively.

It may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen should increased symptoms of psychosis or shift to manic symptomatology occur.

Use with great caution in young and elderly, as such patients are likely to show toxic effects, especially agitation, confusion or postural hypotension.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in hepatic/renal impairment: Use with caution in patients with hepatic and/or renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs metabolised by cytochrome P450 (CYP) 2D6: Doxepin, like other tricyclic antidepressants (TCAs), is metabolised by CYP2D6. Inhibitors or substrates of CYP2D6 (e.g. quinidine, selective serotonin reuptake inhibitors [SSRIs]) may increase the plasma concentration of TCAs when administered concomitantly. The extent of interaction depends on the variability of effect on CYP2D6 and the therapeutic index of the TCA. The clinical significance of this interaction with doxepin has not been systematically evaluated.

MAO inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with doxepin. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Alcohol, antidepressants and anxiolytics: Combined use with other antidepressants, alcohol or anti-anxiety agents should be undertaken with due recognition of the possibility of potentiation. Patients should be cautioned that they may experience an increased sedative effect when tricyclic antidepressants are given with alcohol and anxiolytics.

Cimetidine: has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants.

Sympathomimetics: Sinequan should not be given with sympathomimetic agents such as ephedrine, isoprenaline, noradrenaline, phenylephrine and phenlpropanolamine.

General anaesthetics and local anaesthetics (containing sympathomimetics): When given during tricyclic or tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension, or hypertension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated.

Antihypertensives: Sinequan may decrease the antihypertensive effect of agents such as debrisoquine, bethanidine, guanethidine and of centrally acting antihypertensives such as methyldopa and clonidine. It usually requires daily doses of Sinequan in excess of 150mg before any effect on the action of guanethidine is seen. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Thyroid hormone: The dose of thyroid hormone medication may need reducing if Sinequan is being given concurrently.

Opioid Analgesics: There is possible increased risk of sedative effects when tricyclic antidepressants are given with opioid analgesics such as nefopam. The risk of central nervous system (CNS) side effects is increased when tricyclic antidepressants are given with tramadol.

Sublingual nitrates Sinequan may reduce the effect of sublingual nitrates (owing to dry mouth).

Tolazamide: A case of severe hypoglycaemia, 11 days after the addition of doxepin (75mg/day) has been reported in a non-insulin dependent diabetic patient maintained on tolazamide (1g/day).

Antiarrhythmics: Administration with antiarrhythmics (particularly if the 1A type) may lead to potentiation of cardiac arrhythmias.

Risk of arrhythmias: There is increased risk of arrhythmias when tricyclic antidepressants are used with moxifloxacin, terfenadine or antipsychotic agents. Avoid concomitant use with moxifloxacin and terfenadine.

Plasma Concentrations: Disulfiram, methylphenidate, antipsychotic agents or ritonavir may increase the plasma concentration of tricyclic antidepressants while rifampicin or barbiturates may decrease the plasma concentration.

Other drugs affected by tricyclic antidepressants: Concomitant use with amphetamines or baclofen may cause potentiation of the effects of such drugs. Concomitant use with anticonvulsants may either cause potentiation or reduction of their effects.

Oestrogens: Oestrogens may reduce the effects but increase the possibility of side effects of tricyclic antidepressants.

Other possible interactions: there is a possible increased risk of antimuscarinic side effects when tricyclic antidepressants are given with antimuscarinic agents, antihistamines or clozapine; sedation when given with antihistamines; CNS side effects when given with sibutramine.

4.6 Pregnancy and lactation

Sinequan should only be used in pregnancy if considered essential by the physician. Doxepin crosses the placenta. Use of high doses in animals has resulted in embryotoxicity and some behavioural effects have occurred in neonates. Since there is insufficient experience in pregnant women who have received this drug, its safety in pregnancy has not been established.

Doxepin and its active metabolite desmethyldoxepin are excreted in breast milk. There has been a report of apnoea and drowsiness occurring in a nursing infant whose mother was taking doxepin. The use of Sinequan is contra-indicated during lactation.

4.7 Effects on ability to drive and use machines

Sinequan may cause drowsiness or affect concentration. Patients receiving this medication should be warned of the possibility and cautioned against driving or operating machinery whilst taking this drug.

4.8 Undesirable effects

Sinequan is well tolerated. Most side-effects are mild and generally disappear with continued treatment, or if necessary a reduction in dose.

Note:

Some of the side-effects noted below have not been specifically reported with Sinequan. However, due to the close pharmacological similarities amongst the tricyclics, the reactions should be considered when prescribing Sinequan.

The most common side-effects to Sinequan are drowsiness, dry mouth and constipation. For further details see below under central nervous system and anticholinergic effects.

Anticholinergic effects:

Anticholinergic effects are relatively common and may occur immediately following the first dose of a tricyclic antidepressant. Dry mouth and constipation are the most common anticholinergic effects. Blurred vision and sweating occur occasionally. Urinary retention is rare except in predisposed males who have an enlarged prostate gland. Tolerance is often achieved if treatment is continued. If these undesirable effects do not subside with continued therapy, or if they become severe, it may be necessary to reduce the dosage.

Central nervous system effects:

Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, agitation, numbness or paraesthesiae, tremor (which is usually mild). But at high doses, in susceptible individuals (particularly the elderly) other extrapyramidal symptoms may occur including tardive dyskinesia. Rarely reported are hallucinations, ataxia (generally where mixtures of CNS drugs have been given), and convulsions. Convulsions are unlikely except in people predisposed to seizure activity by brain damage or alcohol and drug abuse.

Psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants.

Cardiovascular:

Cardiovascular effects including postural hypotension, hypertension and tachycardia have been reported occasionally and changes in ECG parameters (widening of the QRS and OR interval) very rarely.

Allergic:

Allergic reactions to tricyclic antidepressants are uncommon. They include skin rash, facial oedema, photosensitisation and pruritus.

Haematological:

Rare cases of eosinophilia and bone marrow depression manifesting as agranulocytosis, leucopenia, thrombocytopenia and purpura.

Gastro-intestinal:

Nausea, vomiting, indigestion, taste disturbances, diarrhoea, anorexia and aphthous stomatitis have been reported. (See Anticholinergic effects).

Endocrine:

Occasional reports of raised or lowered libido, testicular swelling, raised or lowered blood sugar levels. Rarely the syndrome of inappropriate antidiuretic hormone secretion, gynaecomastia, enlargement of breasts and galactorrhoea in the female.

Other: Dizziness, weight gain, chills, fatigue, weakness, flushing, alopoecia, headache, exacerbation of asthma and hyperpyrexia (in association with chlorpromazine) have been occasionally observed. Rare reports of jaundice and of tinnitus.

Withdrawal:

Withdrawal symptoms may occur on abrupt cessation of tricyclic antidepressant therapy and include insomnia, irritability, nausea, headache, malaise and excessive perspiration. Withdrawal symptoms in neonates whose mothers received tricyclic antidepressants during the third trimester have also been reported and include respiratory depression, convulsions and “jitteriness” (hyper-reflexia).

4.9 Overdose

Signs and symptoms:

1. Mild: drowsiness, stupor, blurred vision, excessive dryness of mouth.

2. Severe: respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Als urinary retention (bladder atony), decreased gastro-intestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

Deaths have been reported involving overdoses of doxepin. The reported cases involved doxepin alone and in combination with other drugs and/or alcohol.

Management and treatment:

1. Mild: observation including ECG monitoring and supportive therapy is all that is usually necessary.

2. Severe: medical management of severe Sinequan overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage with appropriate precautions to prevent pulmonary aspiration should be performed even though Sinequan is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. ECG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate anti-arrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1mg to 3mg of physostigmine salicylate.

Because physostigmine is rapidly metabolised, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy. However, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of Sinequan.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The mechanism of action of Sinequan is not definitely known. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on

the adrenergic activity at the synapses so that deactivation of noradrenaline by reuptake into the nerve terminals is prevented. In animal studies anticholinergic, antiserotonergic and antihistaminergic effects on smooth muscle have been demonstrated. At higher than usual clinical doses, adrenaline response was potentiated in animals. This effect was not demonstrated in humans.

5.2 Pharmacokinetic properties

Doxepin is well absorbed from the gastrointestinal tract. Approximately 55-87% of orally administered doxepin undergoes first pass metabolism in the liver, forming the primary active metabolite desmethyldoxepin.

In healthy volunteers, a single oral dose of 75mg resulted in peak plasma concentrations for doxepin ranging from 8.8-45.8 ng/ml (mean 26.1 ng/ml). Peak levels were reached between 2 and 4 hours (mean 2.9 hours) after administration. Peak levels for the primary metabolite desmethyldoxepin ranged from 4.8-14.5 ng/ml (mean 9.7 ng/ml) and were achieved between 2 and 10 hours after administration. The mean apparent volume of distribution for doxepin is approximately 20 L/Kg. The protein binding for doxepin is approximately 76%.

In healthy volunteers, the plasma elimination half-life of doxepin ranged from 8 to 24 hours (mean 17 hours). The half-life of desmethyldoxepin ranged from 33-80 hours (mean 51 hours). Mean plasma clearance for doxepin is approximately 0.84 L/kg.hr. Paths of metabolism of doxepin include demethylation, N-oxidation, hydroxylation and glucuronide formation. Doxepin is excreted primarily in the urine, mainly as its metabolites, either free or in conjugate form.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sinequan 75mg capsule.

Maize starch (dried)
Magnesium stearate
Sodium laurilsulfate

Capsule shell constituents

Gelatin
Erythrosine (E127)
Patent blue V (E131)
Quinoline yellow (E104)
Titanium Dioxide (E171)

Printing ink

Opacode S-1-8215-W-V, Grey

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

Sinequan 75mg capsules are available as:
Packs of 28 capsules. Aluminium/PVC blister strips: 2 rows of 7 capsules per strip, 2 strips in a carton box.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 19/15/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th September 1977

Date of last renewal: 30th September 2002

10 DATE OF REVISION OF THE TEXT

26th January 2005