IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0002/015/001
Case No: 2047146

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

Bristol-Myers Squibb Pharmaceuticals Ltd

Swords, **Co. Dublin**, **Ireland**

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

Motival Tablets

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 **27/03/2008**.

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

Motival Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Nortriptyline Hydrochloride equivalent to 10mg nortriptyline base.
Fluphenazine Hydrochloride 500micrograms.

Excipients
Also includes 63.4mg lactose per tablet. Also includes sucrose and castor oil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet (Tablet).

Pink, sugar-coated, biconvex, triangular tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of patients suffering from mixed anxiety depressive states.

4.2 Posology and method of administration

Adults
One tablet three times daily. If no response has occurred in 4 weeks, alternative therapy should be used. Duration of treatment should not exceed 3 months.

Elderly
This formulation is not indicated for the treatment of patients over 60 years of age.

Children
This formulation is not indicated for the treatment of children.

4.3 Contraindications

Use in children.

Use in patients who are receiving, or who have received within two weeks, monoamine oxidase inhibitors.

Use in patients with epilepsy or organic brain damage.

Use in patients with blood dyscrasias, severe cardiac insufficiency, renal or hepatic dysfunction.

Use in patients hypersensitive to any of the ingredients.

Use in patients during the acute recovery period after myocardial infarction.

4.4 Special warnings and precautions for use

Patients receiving therapy with this product should be kept under regular surveillance by the physician with particular attention to effects on cerebral function, haemopoiesis, and liver function. Motival is associated with a risk of cardiovascular adverse events in all age groups.

Motival should be used with caution in patients with cardiovascular disease or family history of QT prolongation.

The product should only be used with great caution in patients with myocardial insufficiency, severe atherosclerosis, Parkinsonism or extra pyramidal disease or with glaucoma or those on electroconvulsive therapy. Avoid the concomitant use of neuroleptics.

Administration of any phenothiazine may result in extrapyramidal effects and prolonged use may lead to persistent or tardive dyskinesia, particularly in the elderly. (See also section 4.8 Undesirable Effects).

Motival should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.3). Studies in depression of this age group did not show a beneficial effect for tricyclic antidepressants. Studies with other classes of antidepressants have shown a risk of suicidality, self-harm and hostility related to these compounds. This risk cannot be excluded with Motival. Furthermore, long-term safety in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see also sections 4.8 Undesirable Effects and section 4.9 Overdose).

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

4.5 Interaction with other medicinal products and other forms of interaction

Clinical evaluation of Motival has not revealed any drug interactions peculiar to the combination. However, as with other tricyclic antidepressants and phenothiazines, caution is advised with coprescribing of the following:

Anti-arrhythmic agents	Increased risk of ventricular arrhythmias
Anti-convulsants	Anticonvulsant action may be impaired
CNS depressants	Exaggerated or attenuated effects
Other anti-depressants	CNS excitation and hypertension with MAOIs and plasma concentrations of some tricyclics increased by SSRIs
Anti-hypertensive	Additive or attenuated activity
Anti-cholinergic/ Anti-muscarinics	Exaggerated response.
Sympathomimetic	Risk of hypertension and arrhythmias.
Cimetidine	Altered plasma concentration, increased nortriptyline, reduced phenothiazines.
Anti-coagulants	Tricyclics and phenothiazines may alter anticoagulant effects.
Levodopa	Impairment of anti-parkinsonian effect.
Antacids, Anti-diarrhoeals	May alter absorption.
Methylphenidate	Paranoid ideation may occur with tricyclics.
Lithium	Neurotoxicity has been reported with anti-psychotics.
Drugs causing electrolyte imbalance, prolonging the QT interval, or metabolic Inhibitors	Potential for cardiotoxicity.

4.6 Pregnancy and lactation

Use in Pregnancy
Do not use during pregnancy, especially the first and last trimesters, unless there are compelling reasons. There is no evidence as to drug safety in human pregnancy nor are the results of animal studies conclusive.

Nursing Mothers
Breast feeding is not recommended during treatment with Motival.

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 include anti-cholinergic effects such as dry mouth, tachycardia, hypotension, nasal congestion; occasionally, blurred vision, cataract formation, blood dyscrasia, including agranulocytosis, and potential susceptibility to infection. There have been reports of retinopathy, pigmentary retinal deposits and unexplained death in patients receiving fluphenazine at high doses or for prolonged periods.

In common with other anti-psychotics, fluphenazine has been associated with persistent dyskinesia. Tardive dyskinesia may develop in some patients on long term therapy, possibly in relation to total cumulative dose, or may develop after drug therapy has been discontinued. The risk is reported to be greater in elderly patients on high-dose therapy.

Characteristic symptoms are rhythmical involuntary movements of the tongue, face, mouth or jaw, sometimes accompanied by involuntary movements of the extremities. They may persist for many months or even years and, while they gradually disappear in some patients, they appear to be permanent in others.

At first signs of tardive dyskinesia which may be orofacial dyskinesia, the benefit of continued treatment should be carefully assessed against the risk of the development of persistent dyskinesia. Withdrawal of treatment with careful observation of the dyskinesia and psychotic condition has been suggested in order to assess the need for continued neuroleptic therapy and to reveal persisting dyskinesia. Should it be necessary to reinstate treatment, the antipsychotic

agent may mask the syndrome. Anti-parkinsonian agents have proved of little value in this syndrome.

Neuroleptic malignant syndrome
The syndrome may occur with use of any neuroleptic agent. Symptoms include clouding of consciousness, rigidity and other extrapyramidal effects, and autonomic dysfunction, most importantly hyperpyrexia. Treatment involves the immediate cessation of neuroleptic therapy and symptomatic management as appropriate.

As with other neuroleptics, isolated cases of QT prolongation, cardiac arrhythmias (ventricular fibrillation and ventricular tachycardia), sudden unexplained death, cardiac arrest and Torsades de pointes have been reported.

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

4.9 Overdose

It should be treated symptomatically and supportively. If the patient is conscious, prompt gastric lavage, dilution of the stomach contents to delay absorption, or stimulation of vomiting should be attempted. An open airway should be maintained. Extrapyramidal symptoms are amenable to anti-Parkinsonian drugs.

In severe hypotension, all the standard procedures for the management of circulatory shock should be instituted, e.g. vasoconstrictors and/or intravenous fluids. If vasoconstrictors are required, metaraminol, mephentermine or noradrenaline should be administered but not adrenaline, as this will further lower the blood pressure through interaction with the phenothiazine.

Neither nortriptyline nor fluphenazine is removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nortriptyline, the principal active metabolite of amitriptyline, is a tricyclic antidepressant. It possesses some atropine-like properties. It is not a monoamine oxidase inhibitor.

Fluphenazine hydrochloride is a salt of the potent neuroleptic fluphenazine, a phenothiazine derivative of the piperazine type.

5.2 Pharmacokinetic properties

Both nortriptyline and fluphenazine are metabolised in the liver and excreted mainly via the kidney. The plasma half-life of fluphenazine in patients given the hydrochloride by mouth has been shown to be approximately 14.7 hours. The mean plasma half-life of nortriptyline is 36 hours (range 18-60 hours).

5.3 Preclinical safety data

No further information is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carnauba wax
Castor oil
Chalk
Curcumin
Calcium hydrogen phosphate dihydrate

Erythrosine (E127)
Gelatin
Lactose
Magnesium stearate
Maize starch
Povidone
Shellac
Sodium benzoate
Sucrose
Talc
Titanium dioxide (E171)
White beeswax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottles with polypropylene, child-resistant closure, containing 100 tablets.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Ltd
Swords
County Dublin

8 MARKETING AUTHORISATION NUMBER

PA 0002/015/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1977

Date of last renewal: 1st April 2007

10 DATE OF REVISION OF THE TEXT

March 2008