IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0048/041/002
Case No: 2060646

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

Bristol-Myers Squibb (Holdings)

T/A Bristol-Myers Pharmaceuticals, **Swords**, **Co. Dublin**, **Ireland**

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

Buspar 10 mg Tablets

the particulars of which are set out in 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 **12/12/2008**.

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

Buspar 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contain: buspirone hydrochloride 10 mg

Excipients: Contains Lactose Anhydrous DC 111.4mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White pillow-shaped biconvex tablets with a scoreline and “10” on one face.

The scoreline is to allow breaking for ease of swallowing only.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Buspar is indicated for the short-term management of anxiety disorders and the relief of symptoms of anxiety with or without accompanying depression. Treatment should usually be limited to 4-12 weeks.

4.2 Posology and method of administration

Adults:
Dosage should be adjusted according to response for maximum effect. The recommended initial dose is 5 mg two or three times daily and this may be increased every two to three days. The usual therapeutic dose is 15 to 30 mg daily in divided doses with a maximum recommended dose of 45 mg daily in divided doses with a maximum recommended dose of 45 mg daily in divided doses.

Elderly:
Although there is no evidence from kinetic and clinical studies that buspirone would behave differently in the elderly, there are limited data beyond 4 weeks and at doses above 30 mg/day in this age group. Therefore it is recommended that buspirone be used for short term treatment (up to 4 weeks) in the elderly patient, at a maximum dose normally not exceeding 30 mg daily.

Renal and Hepatic Impairment
In patients with a history of renal or hepatic impairment, Buspar should be used with caution. Dosage should be reduced in renal or hepatic impairment.

Children:
Use in children has not been established.

4.3 Contraindications

1. Patients hypersensitive to any of the ingredients of the formulation.

2. Use in epileptic patients.

3. Use in patients with severe renal impairment, with a creatinine clearance of 20 ml per minute or below, or a plasma creatinine above 200 micro moles/litre.

4. Severe liver impairment.

4.4 Special warnings and precautions for use

Buspirone should only be used with great caution in patients with established or likely basal ganglial lesion.

In controlled studies in healthy volunteers, buspirone in single doses up to 20 mg caused no significant impairment of cognitive or psychomotor functions, unlike the benzodiazepines, diazepam or lorazepam. However, patients should not drive or operate machinery unless the drug has been shown not to affect physical or mental ability. The incidence of drowsiness in controlled clinical trials has been shown to be comparable to placebo unlike the comparative benzodiazepine.

Patients with compromised hepatic and renal function require monitoring and possible dosage adjustments.

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

4.5 Interaction with other medicinal products and other forms of interaction

1. Elevated blood pressure has occurred in patients receiving both buspirone and monoamine oxidase inhibitors (phenelzine and tranylcypromine). Concomitant administration is contraindicated.

2. Concomitant administration of nefazodone to healthy volunteers resulted in significant increases in buspirone C_{MAX} and AUC and decreases in plasma concentrations of buspirone metabolite. It is recommended that the initial dose of buspirone be lowered to 2.5mg and subsequent dose adjustments of either product should be based on tolerance and clinical response.

3. Buspirone does not exhibit cross-tolerance with benzodiazepines and other sedative/hypnotic agents and will not prevent the withdrawal syndrome often seen with cessation of therapy with these agents. Before commencing therapy with buspirone it is advisable to withdraw patients gradually from prior chronic treatment with these drugs.

4. In studies in healthy volunteers, buspirone did not potentiate the psychomotor impairment produced by alcohol, in contrast to a comparative benzodiazepine. However, no data is available on concomitant use of alcohol and buspirone at single doses greater than 20 mg. Therefore alcohol should not be used while the patient is taking buspirone.

5. *In vitro* studies have shown that buspirone does not displace warfarin phenytoin or propranolol from plasma proteins.

6. In a study in normal volunteers, no interaction with amitriptyline was observed. A similar study with diazepam showed a slight increase in metabolite (nordiazepam) levels.

7. Buspirone has been shown *In vitro* to be metabolised by cytochrome P450 3A4 (CYP3A4). This is consistent with the interaction observed between buspirone and substances that inhibit this isoenzyme, e.g. erythromycin, itraconazole and grapefruit juice. In cases where Buspar is likely to be used with a potent inhibitor of CYP3A4 a lower dose of buspirone (e.g. 2.5mg b.i.d.) should be used.

8. Concomitant treatment with either diltiazem or verapamil has been demonstrated to increase plasma buspirone concentration. Subsequent dose adjustments of either Buspar or the calcium antagonist should be based on clinical response.

9. Coadministration of rifampicin with Buspar has been shown to decrease the plasma concentration and pharmacodynamic effects of buspirone.

4.6 Pregnancy and lactation

In some studies, administration of high doses of buspirone to pregnant animals produced effects on survival, birth and weanling weights, although there was no effect on foetal development. Since the relevance of this finding in humans has not been established, Buspar is contraindicated in pregnancy and in lactation.

4.7 Effects on ability to drive and use machines

Patients should be cautioned about driving or using complex machinery until they are reasonably certain that Buspar does not affect them adversely.

4.8 Undesirable effects

Side effects include headache, dizziness, nervousness, excitement, light headedness, nausea and diarrhoea. Tachycardia, palpitations, chest pain, drowsiness, confusion, dry mouth, fatigue and sweating have also been reported rarely. In paediatric trials lightheadedness and somnolence occurred more frequently than with placebo.

4.9 Overdose

There is no specific antidote to Buspar. Buspar is not removed by haemodialysis. The stomach should be emptied as quickly as possible. Treatment should be symptomatic and supportive. The ingestion of multiple agents should be suspected.

Death by deliberate or accidental overdose has not been observed. A dose of 375 mg per day in healthy volunteers produced no significant adverse effects. As maximum dose levels are reached symptoms most commonly observed are: nausea, vomiting, dizziness, drowsiness and miosis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Buspar is an azaspirodecanedione. The exact mechanism of Buspar's anxioselective action is not fully known. It does not act on benzodiazepine receptor sites and lacks sedative, anticonvulsant and muscle relaxant properties.

From animal studies it is known to interact with serotonin, noradrenaline, acetylcholine and dopamine systems of the brain. Buspar enhances the activity of specific noradrenergic and dopaminergic pathways, whereas the activity of serotonin and acetylcholine are reduced.

5.2 Pharmacokinetic properties

Buspar is rapidly absorbed when given orally. It is then subject to considerable first-pass metabolism. Peak plasma levels occur 60-90 minutes after dosing. Plasma concentration is linearly related to dose. Following multiple dosing steady state plasma concentrations are achieved within 2 days. Buspar is 95% protein bound. Buspar is eliminated primarily by liver metabolism. In pharmacokinetic studies mean plasma half-lives varied from 2 to 11 hours.

5.3 Preclinical safety data

No further relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Sodium starch glycollate
Microcrystalline cellulose
Collodial anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The tablets are packed in bottles containing 50 or 100 tablets; blisters containing 21, 30, 60, 84, 90 tablets.

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

No specific requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Holdings Ltd
t/a Bristol-Myers Pharmaceuticals
Swords
Co. Dublin

8 MARKETING AUTHORISATION NUMBER

PA 48/41/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th December 1988

Date of last renewal: 12th December 2008

10 DATE OF REVISION OF THE TEXT

June 2010