Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alprazolam 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg of alprazolam.

Excipient(s) with known effect:
Each tablet contains 92.2 mg of lactose (as monohydrate) and 0.12 mg of sodium benzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.Pink, oblong tablet with a score line and debossed APZM 0.5The tablets can be divided into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of anxiety. Alprazolam should only be used if the disorder is severe or is causing invalidity, or if the patient is experiencing inordinate suffering as a result of the disorder.

4.2 Posology and method of administration

Posology
The treatment period should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The total length of treatment should not exceed 8-12 weeks, including the period of gradual dose reduction. Prolonged treatment may be necessary in certain circumstances, but this should not be done until the patient's condition has been reassessed.

As with all benzodiazepines, physicians should be aware that long-term use might lead to dependence in certain patients.

The optimal dose of alprazolam should be individually determined in accordance with the severity of the symptoms and the patient's response. The lowest dose which can control symptoms should be used. Dose should be reassessed at intervals of no more than 4 weeks. The usual dose is stated below. In the few patients who require higher doses, the dose should be increased cautiously to avoid adverse reactions. When higher dose is required, the evening dose should be increased before the daytime doses.

Patients who have never previously taken psychotropic medicinal products generally require lower doses than patients who have either already been treated with tranquillisers, antidepressants or hypnotic medicinal products or those who are chronic alcoholics. In order to avoid ataxia and over-sedation it is recommended that the lowest effective dose be used.

Adults
Initial dose*: 0.25 mg to 0.5 mg, three times a day
Dose*: 0.5 mg to maximum 3 mg per day in divided doses

Elderly, debilitated patients, or patients with impaired renal or hepatic function disorders
Initial dose*: 0.25 mg, twice or three times a day
Dose*: 0.5 mg to 0.75 mg per day in divided doses: gradually increase the dose if necessary, and if the disease permits.

* If undesirable effects occur, the dose should be reduced.

Paediatric population

Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore use of alprazolam is not recommended.

Method of administration
Oral use

Discontinuation of treatment
The dose should be gradually reduced. It is recommended that the daily dose of alprazolam be reduced at a rate not exceeding 0.5 mg per three days. In some patients, it may indeed be necessary to reduce the dose even more gradually.

4.3 Contraindications

Hypersensitivity to the active substance, benzodiazepines or to any of the excipients listed in section 6.1.

Benzodiazepines are also contraindicated in patients with

- Myasthenia gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe hepatic insufficiency

4.4 Special warnings and precautions for use

Risk from concomitant use of opioids:
Concomitant use of alprazolam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related medicinal products such as alprazolam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe alprazolam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Tolerance
The hypnotic effect can diminish following repeated use over a period of several weeks.

Dependence
Chronic use of benzodiazepines can lead to the development of physical and mental dependence. The risk of dependence is greater as the dose and length of treatment increase. There is also an increased risk in patients with a history of drug and alcohol abuse. Furthermore, pharmacodependency may occur at therapeutic doses and/or in patients with no individualised risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Cases of abuse have also been reported.
Patients receiving alprazolam should be monitored accordingly (see sections 4.2, 4.8 and 4.9).

If there is physical dependence, the suspension of treatment is accompanied by withdrawal symptoms. These may consist of headache and muscle pain, severe anxiety and tension, sleep disorders, restlessness, confusion and irritability. In severe cases the following symptoms occur: depersonalisation, derealisation, hyperacusis, loss of sensation and tingling sensations in the limbs, hypersensitivity to light, sound and touch, hallucinations and epileptic seizures. Withdrawal symptoms can appear several days after the end of treatment.

Rebound insomnia, anxiety and tension
When treatment with Alprazolam is suspended, a transient syndrome can occur in which the symptoms that prompted treatment with a benzodiazepine (or benzodiazepine-like substance) in the first place recur with greater intensity than before. The syndrome can be accompanied by other reactions including mood swings, anxiety or sleep disturbances, insomnia and restlessness. Since the risk of withdrawal symptoms/rebound symptoms is greater following rapid dose reduction or the abrupt suspension of treatment, it is recommended that the dose be reduced gradually (tapering off).

It is suggested that the daily dose of alprazolam be decreased by no more than 0.5 mg every three days. Some patients may require even slower dose reduction.

Duration of treatment
The duration of treatment should be as short as possible (see 4.2) and should not exceed 8-12 weeks, including the so called tapering off period of gradual dose reduction. Prolongation of the duration of treatment should only be considered after re-evaluation of the condition of the patient.

It may be important to inform the patient at the start of treatment that the course of treatment will be limited and to explain clearly how doses will be gradually reduced.

It is important to prepare patients for the occurrence of rebound symptoms in order to avoid as much as possible unease about the occurrence of such symptoms during the cessation of therapy. In the case of benzodiazepines with a short half-life time, there are indications that withdrawal symptoms can occur within the dose interval, especially when a high dose is involved. If benzodiazepines with long half-life times are used, it is important to point out that it is prudent not to switch to benzodiazepines with short half-life times because of the withdrawal symptoms that may occur.

Amnesia
As with other benzodiazepines, Alprazolam can cause anterograde amnesia. This usually occurs several hours after the product has been taken (see also 4.8). To reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours.

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, fits of rage, nightmares, aggravated insomnia, hallucinations, psychoses, inappropriate behaviour, oneiroid delirium and other behavioural disorders occur, when using benzodiazepines. Should this occur, use of the medicinal product should be terminated. Paradoxical reactions occur more often in children and elderly patients.

Specific patient groups
Alprazolam should not be used in patients less than 18 years of age because safety and efficacy has not been established.

The elderly and/or debilitated patients should be treated preferably with a lower than usual dose (see 4.2) to preclude the development of ataxia or oversedation. Use Alprazolam with caution in elderly patients as there is a risk of falls secondary to the myorelexant effects of benzodiazopines.

In patients with chronic respiratory insufficiency a lower dose should be used, given the possibility of respiratory depression.

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency.

Benzodiazepines are contraindicated for the treatment of patients with severe hepatic disorders, since benzodiazepines can promote the development of encephalopathy.
Benzodiazepines are not effective for the primary treatment of psychoses.

In a few cases manic episodes were reported in patients with latent depression.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines are not effective for the primary treatment of severe depression and should not be used alone for the treatment of anxiety associated with severe depression, since suicide could occur in such patients. When administering to severely depressed and suicidal patients it is necessary to take suitable precautions and to prescribe appropriate amounts.

Due to possible anticholinergic undesirable effects benzodiazepines should be used with great caution in patients with acute narrow angle glaucoma or in those patients that may be predisposed.

Benzodiazepines should also be used with the greatest caution in patients with a history of alcohol and drug abuse.

Alprazolam contains lactose, sodium and sodium benzoate
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

This medicinal product contains 0.12 mg sodium benzoate in each tablet. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacodynamic interactions

Psychotropic medicinal products:
Alprazolam should be used with caution when combined with other CNS depressants. Enhancement of the central depressive effect may occur in case of concomitant use with antipsychotics (neuroleptics), anxiolytics/sedatives, some antidepressant agents, opioids, anticonvulsants, sedative H1-antihistamines.
In the case of opioid analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Alcohol:
Combination with alcohol potentates the sedative effect of alprazolam. This will affect patients' ability to drive and use machines.Intake of alcohol should be avoided during treatment with alprazolam.

Special care should be made with drugs depressing respiratory function such as opioids(analgesics, antitussives, substitutive treatments), notably in the elderly people.

Clozapine:
With clozapine there is an increased risk of respiratory and/or cardiac arrest.

Muscle relaxants:
One should be prepared for an increase of the muscle relaxing effect (risk of falls) when alprazolam is used during therapy with a muscle relaxant, especially during the beginning of treatment with alprazolam.

Pharmacokinetic interactions

Since alprazolam is metabolised by certain hepatic enzymes (especially CYP3A4), its effect is enhanced by medicinal products that inhibit these enzymes. Alprazolam should therefore be used with caution in patients taking these medicinal products and a reduction of dosage may be necessary when such medicinal products are concomitantly used.

CYP3A4 inhibitors
Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline or diltiazem.
The co-administration of alprazolam with strong CYP3A4 inhibitors likeazole antifungals (ketoconazole, itraconazole, posaconazole, voriconazole), protease inhibitors or some macrolides (erythromycin, clarithromycin, telithromycin) should be made with caution and a substancial dose reduction considered.

Itraconazole, a potent CYP3A4-inhibitor, increases AUC and prolongs the elimination half-life for alprazolam. In a study where healthy volunteers were given itraconazole 200 mg/day and 0.8 mg alprazolam, the AUC was increased two-three fold, and the elimination half-life was prolonged to about 40 hours. Alterations have also been seen on psychomotor function affected by alprazolam. Itraconazole may enhance the CNS-depressant effects of alprazolam and withdrawal of itraconazole may attenuate the therapeutic efficacy of alprazolam.

Nefazodone, fluvoxamine and cimetidine: Caution is required when using these agents (CYP3A4 inhibitors) and alprazolam concurrently and a possible reduction of the alprazolam dose should be considered.
Nefazodone inhibits CYP3A4 mediated oxidation of alprazolam, which results in a doubling of the plasma concentration of alprazolam and risk of intensified CNS effects.In combination, it is therefore recommended to reduce the alprazolam dosage to one half of the dose.
Fluvoxamine treatment extends the half-life for alprazolam from 20 hours to 34 hours and doubles the alprazolam concentration in plasma. When used in combination, half of the dosage of alprazolam is recommended.
Cimetidine reduces the clearance of alprazolam which may possibly intensify the effect. The clinical significance of the interaction has not yet been determined.

CYP3A4 inducers
A reduced effect of alprazolam might occur in patients taking CYP3A4 inducers like rifampicin, phenytoin, carbamazepine or St John's wort. The plasma alprazolam concentrations in the elimination phase are dependent on certain hepatic enzymes (in particular CYP3A4) for the metabolism and are reduced by medicinal products that induce these enzymes. When St. John's wort therapy or treatment with other CYP3A4 inducing agents is suddenly stopped, overdose symptoms of alprazolam may occur.

Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Short term, low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects.
However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose adjustment or discontinuation of alprazolam.
The effect of alprazolam on the pharmacokinetics of other medicinal products
Digoxin:
Increase of digoxin plasma levels has been reported with concomitant use of 1 mg alprazolam daily, particularly in the elderly. Therefore, patients receiving alprazolam and digoxin concurrently should be closely monitored for signs and symptoms of digoxin toxicity.

Imipramine and desipramine:
It has been reported that concurrent administration of alprazolam (at doses of up to 4 mg/day) with imipramine and desipramine caused the steady state plasma levels of these substances to increase by 31% and 20% respectively. It is not yet known whether these changes are of clinical significance.

Warfarin:
It could not be determined whether there was any effect on prothrombin times and warfarin plasma levels.

No interaction was found with propranolol and disulfiram.

4.6 Fertility, pregnancy and lactation

Pregnancy
The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found an increased risk of oral clefts. The data indicated that the risk of having an infant with an oral cleft after maternal benzodiazepine exposure is less than 2/1000 compared with an expected rate for such defects of approximately 1/1000 in the general population.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of foetal active movements and a variability of foetal cardiac rhythm.
When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half life of the product. At high doses, respiratory depression or apnea and hypothermia in newborn may appear. Moreover, neonatal withdrawal symptoms with hyperexcitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed. The apparition of withdrawal symptoms after birth depends on the half life of the substance.

Alprazolam should not be used during pregnancy unless the clinical condition of the woman requires treatment with alprazolam. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the foetus.The therapeutic indications and posology should be strictly respected.

If alprazolam treatment is necessary during last part of pregnancy, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.

Breast-feeding
Alprazolam passes into breast milk. Accordingly, women are advised not to breastfeed while they are using Alprazolam.

Fertility
No data are available regarding effects of alprazolam on fertility.

4.7 Effects on ability to drive and use machines

Alprazolam has major influence on the ability to drive and use machines. Persons whose functioning involves the ability to carry out keen and continuous observations, alertness so as to make the right decisions and full control over the use of limbs, should be warned that their abilities to are affected by sedation, amnesia, reduced concentration and muscular weakness. If a patient does not get enough sleep the risk of reduced alertness increases.

Patients should be warned of this hazard and advised not to drive or operate machinery during treatment. These effects are potentiated by alcohol (see section 4.5)

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); very rare (< 1/10000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Endocrine disorders	**Not known**	Hyperprolactinaemia*
Metabolism and nutrition disorders	**Common**	Decreased appetite
Psychiatric disorders	**Very common**	Depression
	Common	Confusional state, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*
	Uncommon	Mania* (see section 4.4), hallucination*, anger*, agitation*, dependence
	Not known	Hypomania***,** aggression*, hostility*, thinking abnormal*, psychomotor hyperactivity*, drug abuse
Nervous system disorders	**Very common**	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache
	Common	Balance disorder, coordination abnormal, disturbance in attention, hypersomnia**,** lethargy**,** tremor
	Uncommon	Amnesia
	Not Known	Autonomic nervous system imbalance*, dystonia*
Eye disorders	**Common**	Vision blurred
Gastrointestinal disorders	**Very common**	Constipation, dry mouth
	Common	Nausea
	Uncommon	Vomiting
	Not known	Gastrointestinal disorder*
Hepatobiliary disorders	**Not known**	Hepatitis***,** hepatic function abnormal*, jaundice*
Skin and subcutaneous tissue disorders	**Common**	Dermatitis*
	Not Known	Angioedema*, photosensitivity reaction*
Musculoskeletal and connective tissue disorders	**Uncommon**	Musculoskeletal weakness
Renal and urinary disorders	**Uncommon**	Incontinence*
	Not known	Urinary retention*
Reproductive system and breast disorders	**Common**	Sexual dysfunction*
	Uncommon	Menstruation irregular*
General disorders and administration site conditions	**Very common**	Fatigue, irritability
	Uncommon	Withdrawal syndrome
	Not Known	Oedema peripheral*
Investigations	**Common**	Weight increased, weight decreased
	Not known	Intraocular pressure increased*

*ADR identified post-marketing

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. These can range from mild dysphoria and insomnia to a major syndrome, which may include abdominal and

muscle cramps, vomiting, sweating, tremor and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with alprazolam.

Side effects like drowsiness, sedation, decreased attention, confusion, fatigue, headache, double vision, dizziness, muscle weakness, ataxia, and blurred vision may occur, especially at the beginning of treatment. These symptoms are generally reduced with repeated administration.

Amnesia
Anterograde amnesia can occur even at therapeutic doses and the risk increases at higher doses. Amnesia may be accompanied by inappropriate behaviour (see also section 4.4).

Depression
Previously unnoticed depressions may become apparent, in susceptible individuals, during benzodiazepine use.

Psychiatric and "paradoxical" reactions
Reactions such as restlessness, agitation, irritability, aggression, delusions, fits of rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disorders. Such paradoxical reactions are more likely to occur in children and elderly patients. In case of paradoxical reactions treatment should be stopped.

Dependence
Use of this substance (even at therapeutic doses) can result in the development of physical dependence. Suspension of treatment can therefore lead to withdrawal symptoms and rebound symptoms (see also section 4.4). Cases of psychological dependence can also occur. Instances of abuse have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

General information about toxicity
As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). In the management of overdose with any medicinal product it should be born in mind that multiple agents may have been taken. Treatment should be adjusted accordingly.

Symptoms
An overdose usually takes the form of a depression of central nervous system activity, varying from drowsiness to coma. In mild cases of overdosing the symptoms consist of drowsiness, mental confusion and lethargy. In more severe cases ataxia, hypotonia, hypotension, respiratory depression, in rare cases coma and in very rare cases death.

Management
Soon after ingestion it is advisable to stimulate vomiting if the patient is conscious, or, alternatively, if the patient is subconscious, to perform gastric lavage while protecting the airway by intubation. If emptying of the stomach does not result in an improvement of the patient's condition, activated charcoal should be administered and, if necessary, be left behind in the stomach in combination with a laxative. When the amount taken is known to be large, this still may be effective after a long time forced diuresis or haemodialysis is of no value.

Flumazenil can be useful as an antidote.

For individuals in coma, treatment is largely symptomatic. Measures should be taken to avoid possible complications such as asphyxia due to patients swallowing their tongue or aspiration of the stomach contents. The intravenous administration of liquids can be useful in preventing dehydration.

Especially when combined with other sedatives, supporting the vital functions, in particular respiration, is important.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; benzodiazepine derivates
ATC code: N05BA12

Mechanism of action
Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid which mediates both pre- and post-synaptic inhibition in the central nervous system (CNS).

Alprazolam is an anxiolytic medicinal product. Like other benzodiazepines, in addition to its anxiolytic properties, Alprazolam has sedative, hypnotic, muscle-weakening and anticonvulsive properties.

5.2 Pharmacokinetic properties

Absorption
Alprazolam is rapidly absorbed following oral administration. After oral administration, bioavailability is 80% or more. Maximum plasma levels are reached one to two hours after oral administration.

Distribution
Following a single administration, the plasma levels are directly proportional to the administered dose. The maximum plasma levels observed following a dose of 0.5 mg to 3 mg are 8 to 37 ng/ml. Following several administrations of 1.5 mg to 10 mg/day, the average steady-state level was 18.3 to 100 ng/ml.
In vitro, 70% of alprazolam is bound to serum proteins.

Biotransformation
The most important metabolites of alprazolam present in urine are alpha-hydroxy-alprazolam and a benzophenone derivative. The major metabolites in plasma are alpha-hydroxy-alprazolam and 4-hydroxy-alprazolam.Alprazolam is mainly metabolised by CYP3A4.

The benzophenone derivative is virtually inactive. The biological activity of alpha-hydroxy-alprazolam is comparable with that of alprazolam, while 4-hydroxy-alprazolam is about 10 x less active. The plasma levels of these metabolites are low. Their half-lives appear to be of the same order of magnitude as that of alprazolam. The metabolites therefore make only a limited contribution to the biological activity of Alprazolam.

Elimination
The average half-life of alprazolam is between 12 and 15 hours. Repeated doses may lead to accumulation and this should be borne in mind in elderly patients and those with impaired renal or hepatic function.
Alprazolam and its metabolites are mainly excreted via the urine.

Elderly
In elderly men the mean elimination half-life can be prolonged (approximately 16 h).

Hepatic impairment
The mean elimination half-life is increased with impaired liver function (approximately 19 h).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based in conventional studies on genotoxicity and carcinogenic potential.

In rats administered alprazolam for 24 months a tendency for dose-related increase in number of cataracts and in corneal vascularisation was evident in females and males, respectively. The lesions did not appear until after 11 months of treatment.

In a repeated dose toxicity study (12 months) with high doses p.o. convulsions were observed in dogs, some of which were lethal. Relevance for men is not clear.

There was no evidence of carcinogenic potential as revealed by carcinogenicity studies conducted in rats and mice.

Alprazolam administered to rats and rabbits at high doses caused an increase in birth defects and foetal death.

Prenatal exposure of mice and rats to benzodiazepines, including alprazolam, has been associated with behavioural changes in the offspring. The possible significance of these changes to the human situation is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Docusate sodium
Sodium benzoate (E211)
Starch, pregelatinised (maize starch)
Cellulose, microcrystalline
Lactose monohydrate
Magnesium stearate
Silica, colloidal anhydrous
Erythrosine aluminium lake (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C.Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/Aluminium-blister

10, 20, 30, 40, 50, 60, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/140/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th October 2008Date of last renewal: 23rd December 2011

10 DATE OF REVISION OF THE TEXT