Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Beta – Adalat 20mg/50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg nifedipine and 50 mg atenolol.

Excipient: contains 10.0mg of lactose monohydrate per capsule

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard. (capsule)
Brown – reddish, opaque gelatin capsules overprinted with “BETA – ADALAT ” and the Bayer cross, containing white granules and a pink film-coated, round, biconvex tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of hypertension and of chronic stable angina pectoris where therapy with either a calcium channel blocker or a beta-blocker prove inadequate.

4.2 Posology and method of administration

Adults:
Hypertension: One capsule daily swallowed with water. If necessary, the dosage may be increased to one capsule dosed every 12 hours. Patients can be transferred to the combination from other antihypertensive treatments with the exception of clonidine (see Section 4.4).

Angina: One capsule every 12 hours swallowed with water. Where additional efficacy is necessary, prophylactic nitrate therapy or additional nifedipine may be of benefit.

Elderly:
Dosage should not exceed one capsule daily in hypertension or one capsule twice daily in angina.

The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Children:
There is no paediatric experience with Beta-Adalat and therefore this preparation should not be used in children.

General:
Patients with renal or hepatic insufficiency may require lower dosages of Beta-Adalat, (see Section 4.4).

Nifedipine should not be taken with grapefruit juice (see Section 4.5).

4.3 Contraindications

Beta-Adalat should not be administered to patients with known hypersensitivity to atenolol, nifedipine or other dihydropyridines because of the theoretical risk of cross-reactivity.

Beta-Adalat should not be administered to patients with a history of wheezing or asthma or a tendency to bronchospasm (obstructive respiratory disease/bronchial asthma). (Label warning: Do not use if you have a history of wheezing or asthma.)

Beta-Adalat must not be administered to women capable of child-bearing or to nursing mothers.

Beta-Adalat must not be used in the presence of second or third degree heart block, sick sinus syndrome, sino-atrial block, in patients with evidence of overt heart failure or inadequately treated heart failure or decompensated heart failure, NYHA grades III and IV.

Beta-Adalat should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina pectoris, or during or within one month of a myocardial infarction.

Beta-Adalat should not be used for the treatment of acute attacks of angina.

The safety of Beta-Adalat in malignant hypertension has not been established.

Beta-Adalat should not be used for secondary prevention of myocardial infarction.

Beta-Adalat must not be used in conjunction with other drugs with a cardio-depressant action, e.g. verapamil, as conduction disturbances may ensue.

Beta-Adalat should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see Section 4.5).

Beta-Adalat should not be used in pronounced bradycardia (resting heart rate before treatment less than 50 beats/min), hypotension with systolic pressure less than 90 mm Hg, or in the late stages of circulatory disturbances in the hands and legs or in severe peripheral arterial circulatory disturbances.

Beta-Adalat should not be used in patients with a decline in the pH of the blood (acidosis).

In patients with phaeochromocytoma, Beta-Adalat must be administered only after prior therapy with alpha-blockers.

Beta-Adalat must not be given with simultaneous administration of monoamine oxidase inhibitors (MAO inhibitors).

Beta-Adalat must not be used in patients with marked renal impairment (i.e. creatine clearance below 15 ml/min/1.73m^2, serum creatine greater than 600 micromol/litre).

4.4 Special warnings and precautions for use

Cardiac
Particular care should be taken with patients with conduction defects or whose cardiac reserve is poor. However, in patients already treated with a beta-adrenoceptor antagonist, and/or where signs of cardiac failure have been controlled, Beta-Adalat may be substituted with care if necessary.

Beta-Adalat should only be used with caution in patients with controlled congestive heart failure. Evidence of recrudescence of this condition should be regarded as an indication to discontinue therapy.

Beta-Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Beta-Adalat will not prevent possible rebound effects after cessation of other antihypertensive therapy, (see Section 4.5).

In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta-blockers should be used with caution as aggravation of these disorders may occur.

Care should be taken in prescribing a beta-adrenoceptor blocking drug with Class I anti-dysrhythmic agents such as disopyramide.

One of the pharmacological actions of beta-adrenoceptor blocking drugs is to reduce heart rate. In the rare instances where symptoms may be attributable to the slow heart rate at a dose of one capsule daily, the drug should be discontinued.

Ischaemic pain has been reported in a small proportion of patients within one to four hours of the introduction of nifedipine therapy. Although a "steal" effect has not been demonstrated, patients experiencing this effect should discontinue Beta-Adalat.

Cessation of therapy with a beta-adrenoceptor blocking drug in patients with ischaemic heart disease should be gradual, if necessary initiating replacement therapy at the same time, to prevent exacerbation of angina pectoris.

Caution should be exercised when transferring patients from clonidine to beta-adrenoceptor blocking drugs. If beta-adrenoceptor blocking drugs are given concurrently, clonidine should not be discontinued until several days after withdrawal of the beta-adrenoceptor blocking drug.

Caution should be exercised in patients with severe hypotension (systolic pressure <90 mm Hg) in cases of manifest heart failure and in severe aortic stenosis.

Caution should be exercised in cases of first degree heart block or mild heart failure, NYHA grade II.

Beta-blockers may increase the number and duration of anginal attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Therefore, $beta_1$ selective blockers such as atenolol should be used with care.

Obstructive airways disease
Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should not be administered to patients with reversible obstructive airways disease.

Renal impairment
Dosage should not exceed one capsule daily in patients with renal dysfunction. The use of the combination is contra-indicated in patients with marked renal impairment, (see Section 4.3).

In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.

Hepatic impairment
Care should be taken in patients with marked hepatic impairment. Although no dosage adjustment is suggested from the systemic availability of the monocomponents in patients with cirrhosis, hypertensive patients with clinically significant liver disease have not been studied. Nifedipine is metabolised primarily by the liver and therefore patients with liver dysfunction should be carefully monitored.

Anaesthesia
It is not advisable to withdraw beta-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anaesthetic agents such as ether, cyclopropane and trichloroethylene. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg intravenously).

Diabetes
The use of nifedipine in diabetic patients may require adjustment of their control.

Atenolol may mask some of the symptoms of thyrotoxicosis of hypoglycaemia by inhibition of sympathetic nerve function. The effect of hypoglycaemic agents may be increased, particularly by non-cardioselective beta-blockers. The tachycardia of hypoglycaemia may be modified.

General
The benefits and risks must be carefully considered before drugs containing beta-receptor blockers (such as Beta-Adalat) are used in: patients with a history or family history of psoriasis; patients with a history of severe hypersensitivity reactions and patients on desensitisation therapy (decreased adrenergic counter-regulation).

Whilst nifedipine is contra-indicated in pregnancy, particular care must be exercised when administering nifedipine in combination with i.v. magnesium sulphate to pregnant women.

Co-administration of nifedipine with erythromycin, ketoconazole, itraconazole, fluconazole, fluoxetine, indinavir, nelfinavir, ritonavir, amprenavir and saquinavir may theoretically result in an increase in nifedipine plasma concentrations. Upon co-administration with any of these cytochrome P450 3A4 inhibitors, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see Section 4.5).

Beta-Adalat should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Known Interactions
As with other dihydropyridines, nifedipine should not be taken with grapefruit juice as elevated plasma concentrations occur, due to a decreased first pass metabolism. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice (see Section 4.2).

The antihypertensive effect of nifedipine can be potentiated by simultaneous administration of cimetidine.

When used in combination with nifedipine, serum quinidine levels may be suppressed regardless of dosage of quinidine. Therefore, monitoring of quinidine plasma levels and if necessary adjustment of the quinidine dosage are recommended. The pharmacokinetics of nifedipine may also be altered when used in combination with quinidine. It is therefore recommended to monitor blood pressure, and if necessary reduce the nifedipine dosage.

Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary, an increase of the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment with phenytoin is discontinued.

Beta-Adalat should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see Section 4.3).

Concomitant use of prostaglandin synthease inhibiting drugs (e.g. ibuprofen, indomethacin) may decrease the hypotensive effects of beta-blockers. When Beta-Adalat is administered simultaneously with reserpine, alpha-methyldopa, clonidine, guanethidine, guanfacine, or cardiac glycosides, the heart rate may decline more markedly, and stimulus conduction may be delayed.

Beta-Adalat can increase the plasma levels of digoxin and theophylline. Monitoring is therefore recommended, and in some cases a reduction of the dose may be necessary.

Beta-Adalat should be used with great caution in patients who are receiving concomitant myocardial depressants such as chloroform, lignocaine, procainamide, beta-adrenoceptor stimulants such as isoprenaline, or alpha-adrenoceptor stimulants such as noradrenaline.

If Beta-Adalat is administered simultaneously with another beta-blocker, in addition to a more marked decrease in the blood pressure, heart failure may develop. Simultaneous administration of intravenous beta -receptor blockers must therefore be avoided.

In patients with a hypoglycaemic metabolic disorder simultaneously treated with Beta-Adalat and insulin or oral antidiabetics, normalisation of the condition may be delayed, and the symptom of hypoglycaemia, tachycardia, be masked. Regular monitoring of the blood glucose is therefore necessary.

When Beta-Adalat is administered simultaneously with calcium antagonists of the verapamil or diltiazem type or antiarrhythmics, there may be a more marked decrease in the blood pressure, a decline in the heart rate, and disturbances of heart rhythm. Careful monitoring of the blood pressure and ECG is therefore necessary. Concomitant intravenous administration of calcium antagonists must be avoided during treatment with Beta-Adalat.

As diltiazem decreases the clearance of nifedipine, the combination of both drugs should be administered with caution.

Simultaneous therapy with noradrenaline or adrenaline as well as the administration of MAO-inhibitors can lead to an excessive increase in blood pressure.

Since simultaneous therapy with narcotics or antiarrhythmics adversely affects cardiac output, the anaesthetist should be informed that the patient is being treated with Beta-Adalat. If possible, Beta-Adalat should not be discontinued before the operation. However, it must be borne in mind that in the course of interaction of atenolol with narcotics or antiarrhythmics, cardiac output may be reduced more markedly, since the cardiac depressant effects (negative inotropism) of atenolol with narcotics or antiarrhythmics may be additive.

Neuromuscular blockade by tubocurarines may be potentiated by beta-receptor inhibition.

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid falsely. However, HPLC measurements are unaffected.

Simultaneous administration of cisapride and nifedipine or quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine. Consequently, the blood pressure should be monitored and, if necessary, the nifedipine dose reduced.

Potentiation of the blood pressure-lowering action must be anticipated when Beta-Adalat is used in combination with other antihypertensives or with diuretics, vasodilators, nitrates, narcotics, tricyclic antidepressants, barbiturates or phenothiazines, (see Section 4.4).

<u>Theoretical Interactions</u>

Nifedipine is metabolised via the cytochrome P450 3A4 system and, therefore, there are theoretical interactions for drugs, which are known to inhibit this enzyme system (e.g. erythromycin, ketoconazole, itraconazole, fluconazole, fluoxetine, indinavir, nelfinavir, ritonavir, amprenavir and saquinavir). Although no formal *in vivo* interaction studies have been performed with these drugs, co-administration can be expected to lead to an increase in plasma concentrations of nifedipine. Blood pressure should therefore be monitored and, if necessary, a reduction in the nifedipine dose considered (see Section 4.4).

Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase in nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded. When nefazodone is given together with nifedipine, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Although no formal interaction studies have been performed between nifedipine and carbamazipine, phenobarbitone or valproic acid, these drugs have been shown to alter the plasma concentrations of a calcium channel blocker structurally similar to nifedipine. A change in nifedipine plasma concentrations and hence an alteration in efficacy cannot be excluded.

4.6 Fertility, pregnancy and lactation

Beta-Adalat is contra-indicated in women capable of child-bearing.

The safety of nifedipine for use in human pregnancy has not been established. Evaluation of experimental animal studies has shown reproductive toxicity consisting of embryotoxicity and teratogenic effects at maternally toxic doses.

Beta-Adalat is contra-indicated in nursing mothers, as nifedipine and atenolol may be present in breast milk.

In single cases of *in vitro* fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

Theoretically, beta-blockers such as atenolol cause a decrease in placental blood flow, which can result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in foetus and neonates. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

4.7 Effects on ability to drive and use machines

Reactions to the drug, which vary in intensity from individual to individual, may impair the ability to drive or to operate machinery. This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

4.8 Undesirable effects

Beta-Adalat is well-tolerated. Side effects occur predominantly at the beginning of treatment or at high doses, and are generally mild and transient. In clinical studies, the undesired events reported are usually attributed to the pharmacological actions of its components. The following undesired events, listed by body system, have been reported:

Beta-Adalat

Cardiovascular: flushing; oedema

CNS: headache; dizziness

Digestive system: gastrointestinal disturbance

Others: fatigue

Atenolol monotherapy

Cardiovascular:	disturbances of AV conduction; bradycardia; heart failure deterioration; postural hypotension which may be associated with syncope; cold and cyanotic extremities; in susceptible patients: precipitation of heart block, intermittent claudication, Raynaud's phenomenon (cold extremities)
CNS:	confusion; mood changes; nightmares; psychosis and hallucinations; sleep disturbances of the type noted with other beta-blockers
Digestive system:	dry mouth
Metabolic:	hyperglycaemia which may cause latent diabetes mellitus to become manifest, or lead to deterioration in pre-existing diabetes; should a hypoglycaemic metabolic disorder develop in a patient with diabetes, it must be borne in mind that, under treatment with Beta-Adalat, normalisation of the condition may be delayed and the symptom of hypoglycaemia, tachycardia, be masked
Haematological:	purpura; thrombocytopenia
Skin:	alopecia; psoriasiform skin reactions; exacerbation of psoriasis; skin rashes
Musculo-skeletal:	joint reactions (lupus erythematosus-like syndrome)
Neurological:	paraesthesia; myasthenia
Respiratory:	bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints
Special senses:	visual disturbances; dry eyes
Urogenital:	impotence
Others:	an increase in (ANA) antinuclear antibodies has been observed, however the clinical relevance of this is not clear

Nifedipine monotherapy

Most side-effects are consequences of the vasodilatory effects of nifedipine and usually regress on withdrawal of therapy. Side-effects of nifedipine such as flushing and headache may occur at the beginning of the treatment. They are, however, mostly slight and diminish with continuous use.

Other undesirable effects reported were:

Cardiovascular:	palpitations; tachycardia; syncopal episodes with initial dose due to blood pressure decrease; gravitational oedema; vasodilatation (flush, sensation of warmth, erythromelalgia); hypotension
CNS:	headache; dizziness; asthenia; lethargy; vertigo
Neurological:	paraesthesia; nervousness; tremor; mood changes

Digestive system: altered bowel habit; nausea; feeling of repletion; gingival hyperplasia which usually regresses on withdrawal of therapy; disturbances of liver function such as increased transaminase or intra-hepatic cholestasis; rare cases of hypersensitivity-type jaundice have been reported
Metabolic: initial hyperglycaemia
Skin: pruritus; urticaria; exanthema; erythema; exfoliative dermatitis and photosensitive dermatitis; gynaecomastia in older men on long term therapy, which usually regresses on withdrawal of therapy
Hypersensitivity: systemic allergic reactions
Musculo-skeletal: myalgia
Respiratory: dyspnoea
Special senses: visual disturbances
Urogenital: increased frequency of micturition; impotence may occur rarely
Haemic and lymphatic system: purpura; agranulocytosis

As with other sustained release dihydropyridines, exacerbation of angina pectoris may occur rarely at the start of treatment with sustained release formulations of nifedipine. The occurrence of myocardial infarction has been described although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.

4.9 Overdose

Clinical effects

As far as treatment is concerned, elimination of active substances and the restoration of stable cardiovascular conditions have priority.

The symptoms of overdosage may include bradycardia, hypotension, hypoglycaemia, acute cardiac insufficiency and bronchospasm.

These signs may not be fully manifested until several hours after ingestion.

Treatment

General treatment should include close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma and plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. Intravenous calcium gluconate combined with metaraminol may be beneficial for hypotension induced by nifedipine. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 – 10 microgram/kg/minute by intravenous infusion may be given. Dobutamine, due to its positive inotropic effects could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

For bronchospasm: inhalation of $beta_2$ – stimulants such as salbutamol (2 puffs), or orciprenaline sulphate (0.5-1.0 mg) slowly i.v. For generalised convulsions, administration of diazepam slowly intravenously is recommended.

Other possible treatments in cases of life-threatening intoxication are:

Pacemaker therapy, artificial ventilation and haemodialysis (atenolol) or plasma separation (nifedipine).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC codes:

C08C A55
Selective calcium channel blocker (Dihydropyridine derivative) with mainly vascular effects.
Nifedipine, combinations.

C07F B03
Beta blocking agents, selective, and other antihypertensives.
Atenolol with other antihypertensives

Atenolol is classified as a $beta_1$-selective (cardioselective) beta-adrenoceptor antagonist with no membrane-stabilising activity and no partial agonist activity. It is clearly the most hydrophilic of the currently available beta-blockers, and thus demonstrates poor penetration of cell membrane lipids. Atenolol has marked negative inotropic and chronotropic effects, thereby reducing cardiac output, myocardial oxygen demand, and blood pressure, particularly during exercise.

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembrane influx of calcium ions through the L-type calcium channels into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

The fixed combination of nifedipine 20 mg and atenolol 50 mg is designed for the antihypertensive treatment of patients whose blood pressure is inadequately controlled on monotherapy. This combination of a cardioselective, hydrophilic $beta_1$-adrenoceptor antagonist (atenolol), and a potent, specific calcium antagonist (nifedipine) lowers blood pressure to a greater extent than either of its individual components.

Nifedipine's tendency to increase heart rate and plasma renin activity is counteracted by beta-adrenoceptor blockade, while the tendency of atenolol to increase peripheral resistance is counterbalanced by the vasodilatation and reflex increase in sympathetic tone induced by the calcium antagonist.

There is no evidence of clinically significant negative inotropic, dromotropic or chronotropic effects with the combined use of nifedipine and atenolol in man compared with treatment with atenolol alone. Similarly, the chronic renal pharmacodynamic effects of the fixed combination are not dissimilar to the use of atenolol alone.

5.2 Pharmacokinetic properties

The fixed combination of nifedipine 20 mg (slow release) and atenolol 50 mg is bioequivalent to its individual drug components, and there is no evidence of pharmacokinetic interaction between the two drugs.

In the elderly, the half life of nifedipine alone is increased from approximately 5½ hours to 9 hours, but peak plasma levels are unchanged.

The pharmacokinetics of atenolol 50 mg when dosed in free combination with nifedipine 20 mg (slow release) in the elderly were consistent with the published atenolol experience in demonstrating an approximately 45% increase in systemic bioavailability, with increased blood levels 24 hours after dosing in the elderly.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nifedipine tablets:

Microcrystalline cellulose (E460)
Maize starch
Lactose monohydrate
Polysorbate 80 (E433)
Magnesium stearate (E572)
Hypromellose (E464)
Macrogol 4000
Titanium dioxide (E171)
Red iron oxide (E172)

Atenolol granules:

Magnesium carbonate, heavy
Maize starch
Sodium laurilsulfate
Gelatin
Magnesium stearate (E572)

Capsule shell:

Red iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Printing ink:
Shellac glaze
Titanium dioxide (E171)
Propylene glycol (E1520)
Simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister packs composed of PVC/PVDC foil backed with aluminium foil: 3 years.
Blister packs composed of PP foil backed with aluminium foil: 4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs composed of PP foil, backed with aluminium foil, each containing 28 capsules.

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

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA 1410/26/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 3rd October 2008

10 DATE OF REVISION OF THE TEXT

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