SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NIFEDIPRESS MR 10 Modified release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg nifedipine
Excipient with known effect: lactose monohydrate
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified release tablets

Brownish pink, round, film coated tablet.

4.1 Therapeutic indications

NIFEDIPRESS MR tablets are indicated in adults for the treatment of hypertension and the prophylaxis of chronic stable angina pectoris.

4.2 Posology and method of administration

Posology

The recommended starting dose of NIFEDIPRESS MR is 10 mg every 12 hours swallowed with water with subsequent titration of the dosage according to response. NIFEDIPRESS MR permits titration of initial dosage, which may be adjusted upwards to 40 mg every 12 hours, to a maximum daily dose of 80 mg.

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see Section 4.5).

Duration of treatment

Treatment may be continued indefinitely.

Additional information on special populations

Paediatric population
The safety and efficacy of NIFEDIPRESS MR in children below 18 years of age has not been established. Currently available data for the use of nifedipine in hypertension are described in section 5.1.

Older people (>65 years)
The pharmacokinetics of NIFEDIPRESS MR are altered in the older people so that lower maintenance doses of nifedipine may be required.

Patients with hepatic impairment

Nifedipine is metabolised primarily by the liver and therefore patients with mild, moderate or severe liver dysfunction should be carefully monitored and a dose reduction may be necessary.

The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.4 and 5.2).

Patients with renal impairment
Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment (see section 5.2).

Method of administration

Oral use.
As a rule, tablets must be swallowed whole with a little liquid, either with or without food. NIFEDIPRESS MR tablets should not be taken with grapefruit juice (see Section 4.5).
The tablets should not be crushed, chewed, divided or dissolved.

4.3 Contraindications

NIFEDIPRESS MR contra-indicated in patients with known hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross reactivity. They should also not be used in cases of known hypersensitivity to any of the excipients listed in section 4.4 and 6.1.

They should not be used in women who are or who may become pregnant (see section 4.6).

NIFEDIPRESS MR should not be used in clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction. They should not be used in patients in cardiogenic shock.

NIFEDIPRESS MR should not be used for the treatment of acute attacks of angina, or in patients who have had ischaemic pain following its administration previously.

The safety of NIFEDIPRESS MR in malignant hypertension has not been established.

NIFEDIPRESS MR should not be used for secondary prevention of myocardial infarction.

NIFEDIPRESS MR is contra-indicated in patients with acute porphyria.

NIFEDIPRESS MR should not be used in patients with Kock pouch (ileosetomy after proctocolectomy).

NIFEDIPRESS MR 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).

4.4 Special warnings and precautions for use

NIFEDIPRESS MR is not a beta-blocker and therefore gives no protection against the dangers of abrupt withdrawal of beta-blocking drugs. Withdrawal of any previously prescribed beta-blockers should be gradual, preferably over 8 to 10 days.

NIFEDIPRESS MR may be used in combination with beta-blockers and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension and/or cardiac failure must be borne in mind. NIFEDIPRESS MR will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Nifedipine should be used with caution in patients who are hypotensive (severe hypotension with systolic pressure less than 90 mmHg).

Excessive falls in blood pressure may result in transient blindness. If affected the patient should not attempt to drive or use machinery (see section 4.8).

NIFEDIPRESS MR should be used with caution in patients whose cardiac reserve is poor; in patients with heart failure or significantly impaired left ventricular function. Deterioration of heart failure has occasionally been observed with nifedipine.

The use of NIFEDIPRESS MR in diabetic patients may require adjustment of their diabetic therapy.

In dialysis patients with malignant hypertension and irreversible renal failure with hypovolaemia, a significant drop in blood pressure may occur due to vasodilator effects of nifedipine.

Although a ‘steal’ effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

NIFEDIPRESS MR is not recommended for use during breast-feeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known (see Section 4.6).

In patients with mild, moderate or severe impaired liver function, careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.2 and 5.2). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see Section 4.5).

Drugs, which are inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine are, e.g.:

- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole antimycotics (e.g. ketoconazole)
- the antidepressants nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acid
- cimetidine

Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered (see Section 4.5).

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
For use in special populations see Section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that affect nifedipine
Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (see Section 4.4).

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (see Section 4.3).

Upon co-administration of known inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see Sections 4.2 and 4.4). In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

Drugs increasing nifedipine exposure:
- *macrolide antibiotics (e.g., erythromycin)*
- *anti-HIV protease inhibitors (e.g., ritonavir)*
- *azole anti-mycotics (e.g., ketoconazole)*
- *fluoxetine*
- *nefazodone*
- *quinupristin/dalfopristin*
- *cisapride*
- *valproic acid*
- *cimetidine*
- *diltiazem*

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nifedipine should be monitored and, if necessary, an increase in 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 is discontinued.
Increased plasma levels of nifedipine have been reported during concomitant use of alcohol, cyclosporin, gingko biloba and ginseng.

Enhanced hypotensive effect of nifedipine may occur with: aldesleukin, alprostadil, anaesthetics, antipsychotics, diuretics, phenothiazides, prazosin and intravenous ionic X-ray contrast medium. Profound hypotension has been reported with nifedipine and intravenous magnesium sulphate in the treatment of pre-eclampsia

Drugs decreasing nifedipine exposure:

• rifampicin (see above)
• phenytoin
• carbamazepine
• phenobarbital

Decreased plasma levels of nifedipine have also been reported during concomitant use of St John's Wort.

Effects of nifedipine on other drugs
Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives.
When nifedipine is administered simultaneously with beta-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.
There is an increased risk of excessive hypotension, bradycardia and heart failure with beta-blockers.

Digoxin: The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced.

Quinidine: Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

Tacrolimus: Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.
The plasma concentrations of phenytoin, theophylline, non-depolarising muscle relaxants (e.g. tubocurarine) are increased when used in combination with nifedipine.
Nifedipine may result in increased levels of mizolastine due to inhibition of cytochrome CYP3A4.

Nifedipine may increase the neuromuscular blocking effects of vecuronium.

Drug food interactions
Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. 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. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (see Section 4.2).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Because animal studies show embryotoxicity, and teratogenicity (see section 5.3 Preclinical safety data), NIFEDIPRESS MR is contra-indicated during pregnancy (see section 4.3). Embrytoxicity was noted at 6 to 20 times the maximum recommended dose for NIFEDIPRESS MR given to rats, mice and rebbits, and teratogenicity was noted in rabbits given 20 times the maximum recommended dose for NIFEDIPRESS MR.

There are no adequate and well-controlled studies in pregnant women.

An increase in perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation has been reported, however it is unclear whether these reports are due to the underlying hypertension, its treatment or to a specific drug effect.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

Breast-feeding

Nifedipine is excreted in the breast milk, therefore NIFEDIPRESS MR is not recommended during lactation (see section 4.4).

Fertility

In single cases of *in-vitro* fertilization calcium-antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. Nifedipine should be considered as possible causes if there is no other explanation for unsuccessful fathering.

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 (see Section 4.8). This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

Dizziness and lethargy are potential undesirable effects. If affected do not attempt to drive or use machinery (see section 4.8).

Excessive fall in blood pressure may result in transient blindness. If affected do not attempt to drive or use machinery (see section 4.8).

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine, n = 2,661; placebo, n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine, n = 3,825; placebo, n = 3,840) are listed below: ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%). Most side-effects are consequence of the vasodilatory effect of nifedipine.
The frequencies of ADRs reported with nifedipine containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and rare (≥1/10,000 to < 1/1,000). The ADRs identified only during the

ongoing postmarketing surveillance, and for which a frequency could not be estimated, are listed under “Not known”.

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Blood and Lymphatic System Disorders				Agranulocytosis Leucopenia
Immune System Disorders		Allergic reaction Allergic oedema/angio edema (incl. larynx oedema[1])	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction Systemic allergic reactions
Psychiatric Disorders		Anxiety reactions Sleep disorders	Mood changes	Depression
Metabolism and Nutrition Disorders				Hyperglycaemia
Nervous System Disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/Dysaesthesia	Hypoaesthesia Somnolence Lethargy Cerebral ischemia (due to excessive fall in blood pressure)
Eye Disorders		Visual disturbances		Eye pain Transient blindness (due to excessive fall in blood pressure)
Cardiac Disorders		Tachycardia Palpitations		Chest pain(Angina Pectoris) Myocardial infraction[2] Myocardial ischemia (due to excessive fall in blood pressure)
Vascular Disorders	Oedema(incl. peripheral oedema) Vasodilatation	Hypotension Syncope		Flushing
Respiratory,		Nasal		Dyspnoea

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Thoracic and Mediastinal Disorders		congestion Nosebleed		Pulmonary oedema*****
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Vomiting Gastroesophageal sphincter insufficiency Diarrhoea
Hepatobiliary Disorders		Transient increase in liver enzymes		Jaundice Intra-hepatic cholestasis
Skin and Subcutaneous Tissue Disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura Talengiectasis Erythema multiforme Pemphigoid reaction Exfoliative dermatitis Purpura
Musculoskeletal and Connective Tissue Disorders		Muscle cramps Joint swelling		Arthralgia Myalgia Worsening of myasthenia gravis
Renal and Urinary Disorders		Polyuria Dysuria		Increased frequency of micturition
Reproductive System and Breast Disorders		Erectile dysfunction		Gynaecomastia (long-term therapy)

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
General Disorders and Administration Site Conditions	Feeling unwell	Unspecific pain Chills		Fever

1 = may result in life-threatening outcome
2 = The occurrence of myocardial infraction has been described although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.
* cases have been reported when used as tocolytic during pregnancy (see section 4.6).
In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Reports of nifedipine overdose are limited and symptoms are not necessarily dose-related. Severe hypotension due to vasodilation, and tachycardia or bradycardia are the most likely manifested of overdose.

Metabolitic disturbances include hyperglycemia, metabolic acidosis and hypo- or hyperkalaemia.

Cardiac effects may include heart block, AV dissociation and asystole, and cardiogenic shock with pulmonary oedema.

Other toxic effects include nausea, vomiting, drowsiness, confusion, lethargy, flushing, hypoxia, unconsciousness and coma.

Treatment

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority.
After oral ingestion, gastric lavage is indicated, if necessary, in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.
The benefit of gastric decontamination is uncertain.

1. Consider activated charcoal (50 g for adults, 1 g/kg for children) if the patient presents within 1 hour of ingestion of a potentially toxic amount.

Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release (SR, MR) preparations there is no evidence to support this.

2. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.

3. Consider further doses of activated charcoal every 4 hours if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulfate).

4. Asymptomatic patients should be observed for at least 4 hours after ingestion and for 12 hours if a sustained release preparation has been taken.

Haemodialysis serves no purpose as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with elevation of the feet and plasma expenders. If these measures are ineffective, hypotension may be treated with calcium (10-20 ml of a 10% calcium gluconate solution administered intravenously over 5-10 minutes). If the effects are inadequate, the treatment can be continued, with ECG monitoring. In addition, beta-sympathomimetics may be given, e.g. isoprenaline 0.2 mg slowly i.v. or as a continuous infusion of 5µg/min. If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required.

Additional fluids should be administered with caution to avoid cardiac overload.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Calcium channel blocker (dihydropyridine derivative) with mainly vascular effects (ATC code: C08CA05).

Nifedipine is a specific and potent calcium antagonist of the 1, 4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through slow 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.

In hypertension, the main action of NIFEDIPRESS MR is to cause peripheral vasodilatation and thus reduce peripheral resistance.

In angina, NIFEDIPRESS MR reduce peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing after-load.

Additionally, nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

NIFEDIPRESS MR administered twice-daily provides 24-hour control of raised blood pressure. NIFEDIPRESS MR cause reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, NIFEDIPRESS MR has little or no effect on blood pressure.

Paediatric population:

Limited information on comparison of nifedipine with other antihypertensives is available for both acute hypertension and long-term hypertension with different formulations in different dosages. Antihypertensive effects of nifedipine have been demonstrated but dose recommendations, long term safety and effect on cardiovascular outcome remain unestablished. Pediatric dosing forms are lacking.

5.2 Pharmacokinetic properties

Absorption

After oral administration nifedipine is rapidly and almost completely absorbed. The systemic availability of orally administered nifedipine is 45 – 56% owing to a first pass effect. Maximum plasma and serum concentrations are reached at 1.5 to 4.2 hours with NIFEDIPRESS MR (20 mg tablets). Simultaneous food intake leads to delayed, but not reduced absorption.

Distribution

Nifedipine is about 95% bound to plasma protein (albumin). The distribution half-life after intravenous administration was determined to be 5 to 6 minutes.

Biotransformation

After oral administration nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is excreted in the form of its metabolites predominantly via the kidneys and about 5 – 15% via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1%) in the urine.

Elimination

The terminal elimination half-life is 6 - 11 hours (Nifedipress MR 20 mg), because of delayed absorption. No accumulation of the substance after the usual dose was reported during long-term treatment. In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers. In a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result AUC and Cmax of nifedipine increased

on average by 93% and 64% (Child Pugh A) and by 253% and 171% (Child Pugh B), respectively, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.4).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproduction toxicology

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum, and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). The risk to humans cannot be ruled out if a sufficiently high systemic exposure is achieved, however, all of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and were several times the recommended maximum dose for humans (see Section 4.6).

6.1 List of excipients

Colloidal Anhydrous Silica, Lactose monohydrate, Microcrystalline Cellulose, Polysorbate 80, Starch Pregelatinized, Magnesium Stearate, Hypromellose 2910, Macrogol 6000, Titanium Dioxide (E171), Purified Talc, Iron Oxide Red (E172), Purified Water, Carnauba Wax.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25ºC protected from light.

6.5 Nature and contents of container

Blister pack red PVC/Aluminium

28 tablets
30 tablets
56 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Dexcel®-Pharma Ltd.
2nd Floor, Bourn,
1 Manor House Drive,
Coventry, CV1 2FX, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 14017/0013

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

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10 DATE OF REVISION OF THE TEXT

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