Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nurofen Advance Maximum Strength 400mg oral powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains Ibuprofen 400mg (as Ibuprofen lysinate).

Excipient(s):

Sucrose	1.26g/sachet
Tartrazine	0.0067 mg/sachet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral powder
A white, lemon flavoured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of mild to moderate pain associated with headache, migraine, backache, period pain, dental pain, rheumatic and muscular pain, cold and flu symptoms such as sore throat and fever.

4.2 Posology and method of administration

For oral administration and short-term use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

If in children and adolescents between 12 and 18 years this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted
The patient should consult a doctor if symptoms persist or worsen, or if the product is required in adults for more than 5 days when treating pain and 3 days when treating fever.

Adults, the elderly and children aged over 12 years
Initial dose - one sachet. Then, if necessary, one sachet up to three times a day as required.
Dissolve the contents of the sachet in a glass of water, stir, and then drink immediately.

Leave at least six hours between doses. Do not exceed more than 3 sachets (1200mg) in any 24 hour period.

Special patient groups:

Elderly:
No special dose adjustment is required. Because of the possible undesirable effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.

Renal insufficiency:
No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal

insufficiency, see section 4.3).

Hepatic insufficiency (see section 5.2):
No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).

Children and adolescents:
Not to be given to children under 12 years of age.

4.3 Contraindications

Patients with a known hypersensitivity to ibuprofen, tartrazine (E102) or any of the constituents in the product.

Patients with a history of bronchospasm, asthma, rhinitis, angioedema or urticaria associated with acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs).

History of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV).

In patients with cerebrovascular or other active bleeding.

In patients with coagulation disorders or bleeding diathesis.

In patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

During the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See Section 4.2).

Respiratory:
Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Other NSAID's:
Use with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease:
Systemic lupus erythematosus and mixed connective tissue disease - increased
risk of aseptic meningitis (see section 4.8)
Renal:
Renal impairment as renal function may further deteriorate (see section 4.3 and 4.8).
There is a risk of renal impairment in dehydrated children and adolescents.

Hepatic:
Hepatic dysfunction (see sections 4.3 and 4.8).

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID Therapy.

Clinical trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses (2400 mg daily) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg daily) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) are required.

Consideration should also be exercised before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Impaired female fertility:
There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of the treatment.

Gastrointestinal:
NSAID's should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Gastrointestinal (GI) bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (See Section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid or other drugs likely to increase gastrointestinal risk (See below and 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) or anti-platelet agents such as aspirin (See Section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Nurofen Advance Maximum Strength 400mg Oral Powder should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Nurofen Advance Maximum Strength 400mg Oral Powder in case of varicella.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of ibuprofen with :	**Possible effects:**

Other NSAIDs, including salicylates:	The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).
Digoxin:	The concomitant use of Nurofen Advance Maximum Strength 400mg Oral Powder with digoxin preparations may increase serum levels of these medicinal products. A check of serum-digoxin is not as a rule required on correct use (maximum over 4 days).
Corticosteroids:	Corticosteriods as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal; ulceration or bleeding) (see section 4.3)
Anti-platelet agents:	Increased risk of gastrointestinal bleeding (see section 4.4).
Acetylsalicylic acid (low dose):	Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).
Anticoagulants:	NSAIDs may enhance the effect of anti-coagulants, such as warfarin and heparin (see section 4.4). Monitoring of coagulation state is recommended in case of simultaneous treatment.
Phenytoin:	The concomitant use of Nurofen Advance Maximum Strength 400mg Oral Powder with phenytoin preparations may increase serum levels of these medicinal products. A check of serum-phenytoin levels is not as a rule required on correct use.
Selective serotonin reuptake inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding (see section 4.4).
Lithium:	The concomitant use of Nurofen Advance Maximum Strength 400mg Oral Powder with lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium is not as a rule required on correct use

	(maximum over 4 days).
Probenecid and sulfinpyrazone:	Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.
Diuretics, ACE inhibitors, betareceptor-blockers and angiotensin-II antagonists:	NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor-blockers or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.
Potassium sparing diuretics:	The concomitant administration of Nurofen Advance Maximum Strength 400mg Oral Powder and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).
Methotrexate:	The administration of Nurofen Advance Maximum Strength 400mg Oral Powder within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.
Ciclosporin:	The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain nonsteroidal antiinflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.
Tacrolimus:	The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.
Zidovudine:	Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Sulphonylureas:	Clinical investigations have shown interactions between nonsteroidal anti-inflammatory drugs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood-glucose values is recommended as

	a precaution on concomitant intake.
Quinolone antibiotics:	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
Mifepristone	NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

4.6 Fertility, pregnancy and lactation

Fertility
See section 4.4 regarding female fertility.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, Nurofen Advance Maximum Strength 400mg Oral Powder should not be given unless clearly necessary. If Nurofen Advance Maximum Strength 400mg Oral Powder is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductusarteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

The mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Nurofen Advance Maximum Strength 400mg Oral Powder is contraindicated during the third trimester of pregnancy.

Lactation
Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date, so for short-term treatment with the recommended dose for pain and fever interruption of breast-feeding would generally not be necessary.

4.7 Effects on ability to drive and use machines

As central nervous undesirable effects such as tiredness and dizziness may occur on use of Nurofen Advance Maximum Strength 400mg Oral Powder at high dosage, the ability to react and the ability to take part actively in road

traffic and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

Hypersensitivity reactions have been reported and these may consist of:

a) Non-specific allergic reactions and anaphylaxis
b) Respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
c) Various skin reactions e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)

The following list of adverse effects relates to those experienced with ibuprofen at 400mg per single dose up to 1200mg maximum daily dose, for short term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Please note that within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

< Very common (≥1/10)>
< Common (≥1/100 to <1/10)>
<Uncommon (≥1/1,000 to <1/100)>
<Rare (≥1/10,000 to <1/1,000)>
<Very rare (<1/10,000)>
<not known (cannot be estimated from the available data)>

Infections and infestations	Very rare	Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of nonsteroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal anti-inflammatory drugs. If signs of an infection occur or get worse during use of Nurofen Advance Maximum Strength 400mg Oral Powder the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an anti-infective/antibiotic therapy. The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.
Blood and Lymphatic system disorders	Very rare:	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.
Immune system	Uncommon	Hypersensitivity reactions with skin rashes

disorders		and itching, as well as asthma attacks (possibly with drop in blood pressure)
	Very rare	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).
Psychiatric disorders	Very rare	Psychotic reactions, depression
Nervous System disorders	Uncommon	Headache, dizziness, sleeplessness, tinnitus, tiredness, agitation, irritability
	Very rare	Aseptic meningitis – single cases have been reported very rarely.
Eye disorder	Uncommon	Visual disturbances
Ear and labyrinth disorders	Rare	Tinnitus
Cardiac disorders	Very rare:	Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).
Vascular disorders	Very rare	Arterial hypertension
Gastrointestinal disorders	common:	Abdominal pain, dyspepsia and nausea. Heartburn
	Uncommon :	Diarrhoea, flatulence, constipation and vomiting.
	Very rare:	Oesophagitis, pancreatitis, formation of intestinal diaphragm-like strictures. Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of colitis and Crohn's disease (see section 4.4). The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.
Skin and subcutaneous	Uncommon:	Various skin rashes. Hypersensitivity

tissue disorders		reactions with urticaria and pruritus.
	Very rare:	Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").
Renal and urinary disorders	Rare	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood may also occur rarely.
	Very rare:	Formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency. Renal function should therefore be checked regularly.
Hepatic disorders	Very rare	Liver disorders

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
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

The half-life in overdose is 1.5 - 3 hours.

Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache, dizziness, hypotension and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids; propionic acid derivative
ATC Code: M01A E01

Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine therefore are the same as those of ibuprofen acid.

Ibuprofen is an NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggests that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when a single dose of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane of platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Peak plasma concentration of ibuprofen occurs 1 - 2 hours after administration of ibuprofen acid.

Peak plasma concentration is achieved within 25 minutes for Nurofen Advance Maximum Strength 400mg Oral Powder (400mg ibuprofen lysine) compared with 90 minutes ($p<0.0001$) for 2 x 200mg Nurofen (ibuprofen acid) tablets and 30 minutes ($p=0.0441$) for 2 x 200 mg Nurofen (ibuprofen lysine) tablets.

The mean plasma concentration 4.5 minutes after dosing with Nurofen Advance Maximum Strength 400mg Oral Powder was 8.69 µg/ml (SD 3.12; 95%CI 7.40 - 9.98), while at 9 minutes post-dosing the mean plasma concentration was 20.27 µg/ml (SD 7.37; 95%CI 17.23 - 23.32).

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.

Elimination half-life is approximately 2 hours.

No significant differences in pharmacokinetic profile are observed in the elderly.

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastro-intestinal tract. In vitro and in vivo studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found. Ibuprofen led to inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat and mouse). Experimental studies have demonstrated that ibuprofen crosses the placenta, for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex
Lemon essence (containing natural flavouring substances and preparations, maltodextrin, modified maize starch and tartrazine E102)
Saccharin sodium (E954),
Sodium cyclamate (E952)
Sodium citrate (E331)
Sucrose

6.2 Incompatibilities

The reconstituted solution should not be mixed with other medicinal products.

6.3 Shelf life

As packaged from date of manufacture: 3 years.
Once the solution is prepared, use immediately.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-dose sachet made of a heat-sealable paper/aluminium sheet /polythene complex or polyester/polyethylene/aluminium/polyethylenethylene laminate in an outer cardboard carton.

Pack sizes: 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15 and 16 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Instructions for reconstitution are included in section 4.2

The appearance of the solution is colourless, clear to translucent with no solid particulates.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Ireland Ltd
7 Riverwalk,
Citywest Business Campus,
Dublin 24,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0979/032/014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd March 2012

10 DATE OF REVISION OF THE TEXT

January 2016