Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Niaspan 500 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 500mg nicotinic acid.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

White to off-white capsule-shaped tablet. Each tablet is embossed with the tablet strength on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia, characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol, and in patients with primary hypercholesterolaemia. Niaspan should be used in patients in combination with HMG-CoA reductase inhibitors (statins), when the cholesterol lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate. Niaspan can be used as monotherapy only in patients who do not tolerate HMG-CoA reductase inhibitors. Diet and other non-pharmacological treatments (e.g. exercise, weight reduction) should be continued during therapy with Niaspan.

4.2 Posology and method of administration

Niaspan should be taken at bedtime, after a low-fat snack (e.g. an apple, low fat yoghurt, slice of bread) and doses should be individualised according to the patient's response.

Initial dose
Therapy with Niaspaṇ must be initiated with a low dose and increased gradually.

The recommended dose escalation schedule is shown below in Table 1:

Table 1: Dose escalation schedule

	Week(s)	Dosage		Daily nicotinic acid dose
⇑ INITIAL TITRATION SCHEDULE ⇓	1	Niaspan 375mg	1 tablet at bedtime	375mg
	2	Niaspan 500mg	1 tablet at bedtime	500mg
	3	Niaspan 750mg	1 tablet at bedtime	750mg
	4-7	Niaspan 500mg	2 tablets at bedtime	1000mg
		Niaspan 750mg	2 tablets at bedtime	1500mg
		Niaspan 1000mg	2 tablets at bedtime	2000mg

Maintenance dose
The recommended maintenance dose is 1000 mg (two 500 mg tablets) to 2000 mg (two 1000 mg tablets) once daily at bedtime depending on the patient's response and tolerance. If the response to 1000 mg daily is inadequate, the dose may be increased to 1500 mg daily and subsequently to 2000 mg daily.

The daily dosage of Niaspan should not be increased by more than 500mg in any four-week period after the initial titration to 1000 mg. The maximum dose is 2000 mg per day.

The different Niaspan tablet strengths have different bioavailability and are therefore not interchangeable.

Niaspan must not be replaced with other nicotinic acid preparations, see section 4.4.

In patients previously treated with other nicotinic acid products, Niaspan treatment must be initiated with the recommended Niaspan dose escalation schedule. The maintenance dose should subsequently be individualised according to the patient's response.

If Niaspan therapy is discontinued for an extended period, re-institution of therapy must include a dose escalation.

Niaspan tablets must not be broken, crushed or chewed before swallowing.

Renal impairment
No studies have been performed in patients with impaired renal function, Niaspan must be used with caution in patients with renal disease.

Hepatic impairment
No studies have been performed in patients with impaired hepatic function. Niaspan must be used with caution in patients with a history of liver disease and who consume substantial quantities of alcohol, see section 4.4. Niaspan is contraindicated in patients with significant hepatic dysfunction, see section 4.3.

Elderly
No dose adjustment is necessary.

Children
The safety and efficacy of nicotinic acid therapy in children and adolescents has not been established. Use in children and adolescents is not recommended.

4.3 Contraindications

Niaspan is contraindicated in patients with

- hypersensitivity to nicotinic acid or to any of the excipients, see section 6.1,
- significant hepatic dysfunction,
- active peptic ulcer disease,
- arterial bleeding.

4.4 Special warnings and precautions for use

Niaspan must not be replaced with other nicotinic acid preparations. When switching from other nicotinic acid preparations to Niaspan, therapy with Niaspan must be initiated with the recommended dose escalation schedule, see section 4.2.

Liver

Nicotinic acid preparations have been associated with abnormal liver tests. Severe hepatic toxicity, including fulminant hepatic necrosis, has occurred in patients who have taken long-acting nicotinic acid products in place of immediate-release nicotinic acid. Since the pharmacokinetics of Niaspan are different to other nicotinic acid preparations, Niaspan must not be replaced with other preparations. The prescribing information of the HMG-CoA reductase inhibitor should also be consulted for warnings and precautions for use.

Caution is advised when Niaspan is used in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Elevated liver transaminases have been observed with Niaspan therapy. However, transaminase elevations were reversible upon discontinuation of Niaspan.

Liver tests including AST and ALT must be performed periodically in all patients during therapy with Niaspan and prior to treatment in case of history and/or symptoms of hepatic dysfunction (e.g. jaundice, nausea, fever, and/or malaise). If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal, the drug must be discontinued.

Skeletal muscle

Reports of rhabdomyolysis in patients on combined therapy with Niaspan and HMG-CoA reductase inhibitors have been received from spontaneous reporting. Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and Niaspan should carefully weigh the potential benefits and risks and should carefully monitor patients for any symptoms of rhabdomyolysis e.g., muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations.

A CPK level should be measured before starting such a combination in patients with pre-disposing factors for rhabdomyolysis, as follows:

- renal impairment
- hypothyroidism
- alcohol abuse
- age > 70 years

- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with fibrate or HMG-CoA reductase inhibitor

Muscle damage must be considered in any patient presenting with diffuse myalgia, muscle tenderness and/or marked increase in muscle CK levels (> 5 x ULN); under these conditions treatment must be discontinued.

The prescribing information of the HMG-CoA reductase inhibitors should be consulted.

Glucose Intolerance

Diabetic or potentially diabetic patients should be observed closely since there may be a dose-related increase in glucose intolerance. Adjustment of diet and/or oral antidiabetics and/or insulin therapy may become necessary.

Unstable angina and acute myocardial infarction

Caution is advised when Niaspan is used in patients with unstable angina or in the acute phase of myocardial infarction, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Uric acid

Elevated uric acid levels have occurred with Niaspan therapy. Monitoring of patients predisposed to gout is recommended.

Coagulation

Niaspan may affect platelet count and prothrombin time, see section 4.5. Patients undergoing surgery should be carefully evaluated. Caution is also advised when Niaspan is administered concomitantly with anti-coagulants; patients receiving anti-coagulants must be monitored closely for prothrombin time and platelet count.

Hypophosphataemia

Niaspan has been associated with reductions in phosphorous levels. Although these reductions were transient, monitoring of phosphorous levels is recommended in patients at risk of hypophosphataemia.

Other

Patients with a history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during Niaspan therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant alcohol or hot drinks may increase undesirable flushing and pruritus and should be avoided around the time of Niaspan ingestion.

Niaspan has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000 mg). In addition, Niaspan has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%).

When Niaspan is administered concomitantly with anti-coagulants, prothrombin time and platelet counts must be monitored closely.

Nicotinic acid may potentiate the blood-pressure lowering effect of ganglionic blocking agents e.g. transdermal nicotine or vasoactive drugs such as nitrates, calcium channel blockers or adrenergic blocking agents.

Bile acid sequestrants bind to other orally administered medicinal products and should be taken separately, see also

prescribing information of the concerned product.

Nicotinic acid may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Nicotinic acid may also give false-positive reactions with cupric sulphate solution (Benedict's reagent) in urine glucose tests.

Combination of nicotinic acid with HMG-CoA reductase inhibitors may increase the risk for myopathy and rhabdomyolysis, see also section 4.4. The prescribing information of the HMG-CoA reductase inhibitor should also be consulted.

4.6 Fertility, pregnancy and lactation

Pregnancy

It is not known whether nicotinic acid at doses typically used for lipid disorders can cause foetal harm when administered to pregnant women or whether it can affect reproductive capacity. Animal studies are incomplete, see section 5.3.

Niaspan should not be prescribed to pregnant women unless strictly necessary.

Lactation

Nicotinic acid has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. No studies have been conducted with Niaspan in nursing mothers.

4.7 Effects on ability to drive and use machines

Niaspan has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Flush

In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events for Niaspan (reported by 88% of patients). In these studies fewer than 6% of Niaspan patients discontinued due to flushing.
In comparisons of immediate-release (IR) nicotinic acid and Niaspan, although the number of patients who flushed was similar, fewer flushing episodes were reported by patients who received Niaspan. Following four weeks of maintenance therapy with Niaspan at daily doses of 1500 mg, the frequency of flushing over the four week period averaged 1.88 events per patient.

Flushing reactions generally occur during early treatment and the dose titration phase. They are thought to be mediated by the release of prostaglandin D2 and tolerance to flushing usually develops over the course of several weeks.

Spontaneous reports suggest that in rare cases, flushing may be more severe and accompanied by symptoms of dizziness, tachycardia, palpitations, dyspnoea, sweating, chills, and/or oedema, which in rare cases may lead to syncope. Medical treatment should be administered as necessary.

Hypersensitivity reactions

Hypersensitivity reactions have been reported very rarely. These may be characterised by symptoms such as

generalised exanthema, flush, urticaria, vesiculobullous rash, angioedema, laryngospasm, dyspnoea, hypotension, and circulatory collapse. Medical treatment should be administered as necessary.

The following adverse reactions have been observed in clinical studies or in routine patient management, in patients receiving the recommended daily maintenance doses (1000, 1500, and 2000 mg) of Niaspan. They are presented by system organ class and frequency grouping (very common >1/10; common >1/100, <1/10; uncommon >1/1,000, <1/100; rare >1/10,000, <1/1,000; very rare <1/10,000, including isolated reports).
In general, the incidence of adverse reactions was higher in women compared to men. (Please refer to Table 2 below)

Table 2: Adverse reactions

Organ class	**Very common >1/10**	**Common >1/100, <1/10**	**Uncommon >1/1,000, <1/100**	**Rare >1/10,000, <1/1,000**	**Very rare <1/10,000, including isolated reports**
Immune system disorders					Hypersensitivity
Metabolism and nutrition disorders				Glucose tolerance decreased	Anorexia, gout
Psychiatric disorders				Insomnia, nervousness	
Nervous system disorders			Headache, dizziness	Syncope, paraesthesia	Migraine
Eye disorders				Visual impairment	Amblyopia, cystoid macular oedema
Cardiac disorders			Tachycardia, palpitations		Atrial fibrillation, arrhythmia
Vascular disorders	Flushing			Hypotension, orthostatic hypotension	Collapse
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Rhinitis	
Gastro-intestinal disorders		Diarrhoea, nausea, vomiting, abdominal pain, dyspepsia		Flatulence, eructation	Peptic ulcers
Hepatobiliary disorders					Jaundice
Skin and subcutaneous tissue disorders		Pruritus, rash	Hyperhidrosis, rash generalised urticaria, dry skin	Face oedema, dermatitis bullous, rash maculopapular	Skin hyper-pigmentation, acanthosis nigricans
Musculo-skeletal, connective tissue and bone				Muscle spasms, myalgia, myopathy, myasthenia	

disorders					
General disorders and administration site conditions			Pain, asthenia, chills, oedema peripheral	Chest pain	
Investigations			Aspartate aminotransferase increased; alanine aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, blood amylase increased, blood glucose increased, blood uric acid increased, platelet count decreased, prothrombin time prolonged, blood phosphorus decreased, blood creatinine phospokinase increased		

Adverse reactions from postmarketing experience:
The following adverse reactions have been reported in postmarketing experience with nicotinic acid prolonged release. Adverse reactions are presented by system organ class.

Nervous system disorders: Burning sensation

Eye disorders: Blurred vision

Hepatobiliary disorders: Hepatitis

Skin and subcutaneous tissue disorders: Skin discolouration, skin burning sensation, erythema

General disorders and administration site conditions: Feeling hot

4.9 Overdose

Information on acute overdose with Niaspan in humans is limited. The signs and symptoms of an acute overdose are anticipated to be those of excessive pharmacological effect: severe flushing, nausea/vomiting, diarrhoea, dyspepsia, dizziness, syncope, hypotension, potential cardiac arrhythmias and clinical laboratory abnormalities including elevations in liver function tests. The patient should be carefully observed and given supportive treatment. Insufficient information is available on the dialysis potential of nicotinic acid.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nicotinic acid, ATC code: C10AD02

Nicotinic acid is a water-soluble B-complex vitamin which is a naturally occurring constituent of foods. The human body is not entirely dependent on dietary sources of nicotinic acid, since it may also be synthesised from tryptophan.

The mechanism of action by which nicotinic acid modify lipid profiles is not fully elucidated. However, it is recognised that nicotinic acid inhibits the release of free fatty acids from adipose tissue resulting in less free fatty acids being presented to the liver. Since fewer fatty acids are being transported to the liver, fewer are esterified to triglycerides and then incorporated into VLDL. This may lead to a decrease in LDL generation. By increasing lipoprotein lipase activity, nicotinic acid may increase the rate of chylomicron triglycerides removal from plasma.

Thus, nicotinic acid decreases the rate of hepatic synthesis of VLDL and subsequently LDL. It does not appear to affect faecal excretion of fats, sterols, or bile acids.

At the recommended maintenance dose, Niaspan (but not nicotinamide) resulted in a clinical reduction in total cholesterol to HDL ratio [-17, to - 27%,], LDL [- 8 to - 16%], triglycerides [- 14 to - 35%] with an increase in HDL [16% to 26%]. In addition to the above mentioned reduction in LDL levels, nicotinic acid causes a shift in LDL composition from the small dense LDL particles (major atherogenic lipoprotein) to the larger, more buoyant LDL particles (less atherogenic). The increase in HDL is also associated with a shift in the distribution of HDL sub-fractions including an increase in the HDL2 to HDL3 ratio, the protective effect of HDL being mainly due to HDL2. Moreover, nicotinic acid increases serum levels of apolipoprotein A1(Apo 1), one of the two major lipoproteins of HDL, while decreases concentrations of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions known to play important roles in atherogenesis. The serum levels of lipoprotein a, [Lp (a)], which present great homology with LDL but considered as an independent risk factor for coronary heart disease, are also significantly reduced by Niaspan.

Data from clinical trials suggest that women have a greater hypolipidaemic response than men at equivalent doses of Niaspan.

There are no specific studies of the combination of Niaspan with statins.

The beneficial effect of Niaspan on morbidity and mortality has not been directly assessed. However, relevant clinical data are available with immediate release (IR) nicotinic acid.

5.2 Pharmacokinetic properties

Absorption
Nicotinic acid is rapidly and extensively absorbed when administered orally (at least 60-76% of dose).

Peak steady-state nicotinic acid concentrations were 0.6, 4.9, and 15.5 microgram/ml after doses of 1000, 1500, and 2000 mg Niaspan once daily (given as two 500 mg, two 750 mg, and two 1000 mg tablets, respectively).

Single-dose bioavailability studies have demonstrated that Niaspan tablet strengths are not interchangeable.

Distribution

Studies using radiolabelled nicotinic acid in mice show that nicotinic acid and its metabolites concentrate in the liver, kidney and adipose tissue.

Metabolism

The pharmacokinetic profile of nicotinic acid is complicated due to rapid and extensive first-pass metabolism which is

species and dose-rate specific. In humans, one pathway (Pathway 1) is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to nicotinic acid. There is evidence to suggest that nicotinic acid metabolism along this pathway leads to flush. The other pathway (Pathway 2) results in the formation of nicotinamide adenine dinucleotide (NAD). A predominance of metabolism down Pathway 2 may lead to hepatotoxicity. It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolised to at least N-methylnicotinamide (MNA) and nicotinamide N-oxide (NNO). MNA is further metabolised to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidaemia, these metabolic pathways are saturable, which explains the non-linear relationship between nicotinic acid dose and plasma concentrations following multiple dose Niaspan administration .

Nicotinamide does not have hypolipidaemic activity; the activity of the other metabolites is unknown.

Elimination

Nicotinic acid and its metabolites are rapidly eliminated in the urine. Following single and multiple doses, approximately 60-76% of the dose administered as Niaspan was recovered in the urine as nicotinic acid and metabolites; up to 12% was recovered as unchanged nicotinic acid after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Gender differences

Steady state plasma concentrations of nicotinic acid and metabolites after administration of Niaspan are generally higher in women than in men, with the magnitude of difference varying with dose and metabolite. Recovery of nicotinic acid and metabolites in urine, however, is generally similar for men and women, indicating the absorption is similar for both genders. The gender differences observed in plasma levels of nicotinic acid and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution.

5.3 Preclinical safety data

Nicotinic acid has been shown to be of low toxicity in customary animal studies.

Female rabbits have been dosed with 0.3 g nicotinic acid per day from pre-conception to lactation, and gave birth to offspring without teratogenic effects. Further specific animal reproduction studies have not been conducted with nicotinic acid or with Niaspan.

In a life-time study in mice, high dose levels of nicotinic acid showed no treatment-related carcinogenic effects and no effects on survival rates.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Povidone
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C

Blisters: Store in the original package to protect from moisture.
Bottles: Keep the bottle tightly closed to protect from moisture.

6.5 Nature and contents of container

Blisters

Niaspan 500 mg prolonged-release tablets are packed in individually sealed strips (PVC/ Chlortrifluoroethylene/ PE/ Aluminium).

Blisters of 7, 10, 14, 20, 21, 28, 30, 50, 56, 60, 84, 90, 91, 98, 100 and 105 tablets are available.

Bottles

The Niaspan 500 mg prolonged-release tablet strength is packaged in tablet containers (white, round, HDPE bottles). Each container is provided with a silica gel desiccant, a purified cotton wool plug, and a 38 mm child-resistant, PP screw closure. Each container holds 100 tablets.

Not all containers or pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ireland Ltd
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8 MARKETING AUTHORISATION NUMBER

PA 38/93/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 April 2004

Date of last renewal: 22 December 2008

10 DATE OF REVISION OF THE TEXT

October 2010