ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pelzont 1,000 mg/20 mg modified-release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 1,000 mg of nicotinic acid and 20 mg of laropiprant.

Excipient(s) with known effect:
Each modified-release tablet contains 128.4 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablet.

Capsule-shaped, white to off-white tablet, with "552" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pelzont is indicated for the treatment of dyslipidaemia, particularly in adult patients with combined mixed dyslipidaemia (characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol) and in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial).

Pelzont 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. It can be used as monotherapy only in patients in whom HMG-CoA reductase inhibitors are considered inappropriate or not tolerated. Diet and other non-pharmacological treatments (e.g. exercise, weight reduction) should be continued during therapy with Pelzont.

4.2 Posology and method of administration

Posology
The starting dose is one modified-release tablet (1,000 mg nicotinic acid/20 mg laropiprant) once a day. After four weeks, it is recommended that patients be advanced to the maintenance dose of 2,000 mg/40 mg taken as two modified-release tablets (1,000 mg/20 mg each) once daily. Daily doses greater than 2,000 mg/40 mg have not been studied and therefore are not recommended.

If Pelzont is missed for less than 7 consecutive days, patients can resume therapy at the last administered dose. If Pelzont is missed for 7 or more consecutive days, therapy should be resumed at the 1,000 mg/20 mg dose for 1 week, before advancing to the maintenance dose of 2,000 mg/40 mg.

Those patients switching from 2,000 mg or more of prolonged-release nicotinic acid can initiate Pelzont at the 2,000 mg/40 mg dose. Patients switching from less than 2,000 mg of prolonged-release nicotinic acid should initiate therapy at the starting dose of 1,000 mg/20 mg and advance to the 2,000 mg/40 mg maintenance dose after four weeks. For patients switching from immediate-release nicotinic acid to Pelzont, therapy should be initiated at the 1,000 mg/20 mg dose and advanced to the 2,000 mg/40 mg maintenance dose after four weeks.

Elderly patients
No dose adjustment is required for elderly patients.

Paediatric population
Safety and effectiveness of Pelzont in paediatric patients under the age of 18 years have not been established. No data are available.

Patients with hepatic or renal insufficiency
Use of Pelzont in patients with hepatic or renal insufficiency has not been studied. Like other nicotinic acid medicinal products, Pelzont is contraindicated in patients with significant or unexplained hepatic dysfunction. It should be used with caution in patients with renal insufficiency, because nicotinic acid and its metabolites are primarily excreted by the kidneys (see sections 4.3, 4.4 and 5.2).

Concomitant therapy
Acetylsalicylic acid provides no additional reduction of flushing beyond that achieved by Pelzont. Therefore, treatment with acetylsalicylic acid to alleviate flushing symptoms is not necessary (see section 5.1).

Because co-administration of bile acid sequestrants may reduce the bioavailability of acidic medicinal products such as nicotinic acid, it is recommended that Pelzont be administered > 1 hour before or > 4 hours after administration of a bile acid sequestrant (see section 4.5).

Method of administration
The tablets should be taken whole, with food, in the evening or at bedtime. To preserve the modified-release properties, the tablets must not be split, broken, crushed, or chewed before swallowing. To reduce the possibility of flushing, drinking alcohol or hot drinks or eating spicy foods should be avoided at the time of ingestion of the medicinal product.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Significant or unexplained hepatic dysfunction.
- Active peptic ulcer disease.
- Arterial bleeding.

4.4 Special warnings and precautions for use

When Pelzont is co-administered with a statin, please refer to the Summary of Product Characteristics for that particular medicinal product.

Hepatic effects
Switching from immediate-release (crystalline) nicotinic acid to Pelzont has not been studied. However, cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have switched from immediate-release nicotinic acid to long-acting nicotinic acid at equivalent doses. Therefore, patients switching from immediate-release nicotinic acid to Pelzont should be initiated at the 1,000 mg/20 mg dose.

Pelzont should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Like other lipid-lowering therapies, nicotinic acid medicinal products have been associated with abnormal liver function tests (see section 4.8). Transaminase elevations were reversible upon discontinuation of therapy.

Liver function tests are recommended before initiation, every 6 to 12 weeks for the first year, and periodically (e.g. semi-annually) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in alanine aminotransferase

(ALT) or aspartate aminotransferase (AST) of ≥ 3 X ULN persist, reduction of dose or withdrawal of Pelzont is recommended.

Effect on skeletal muscle
Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥ 1,000 mg/day) of nicotinic acid and HMG-CoA reductase inhibitors (statins) (see section 4.8).

Physicians contemplating combined therapy with statins and Pelzont should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased. Periodic serum creatine kinase (CK) should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis.
- Age > 70 years
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse.

If muscle pain, weakness or cramps occur while a patient is receiving Pelzont with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped.

Race
In an interim analysis of an ongoing clinical outcome study, an independent safety monitoring committee identified a higher than expected incidence of myopathy in Chinese patients taking Pelzont and simvastatin 40 mg. Therefore, caution should be used when treating Chinese patients with Pelzont co-administered with simvastatin or ezetimibe/simvastatin (particularly simvastatin doses of 40 mg or higher). Because the risk of myopathy with statins is dose-related, the use of Pelzont with simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with Pelzont co-administered with simvastatin or ezetimibe/simvastatin.

Renal dysfunction
Because nicotinic acid and its metabolites are excreted through the kidneys, Pelzont should be used with caution in patients with renal dysfunction.

Effect on glucose
Nicotinic acid medicinal products have been associated with increases of fasting blood glucose levels (see section 4.8). Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycaemic therapy may be necessary.

Acute coronary syndrome
As with other nicotinic acid medicinal products, caution should be used when Pelzont is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive medicinal products such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Haematologic effects
As with other nicotinic acid medicinal products, Pelzont (2,000 mg/40 mg) was associated with small reductions in platelet count (see section 4.8). Therefore, patients undergoing surgery should be carefully evaluated.

Effect on uric acid
As with other nicotinic acid medicinal products, Pelzont (2,000 mg/40 mg) was associated with small increases in uric acid levels (see section 4.8). Therefore, Pelzont should be used with caution in patients with or predisposed to gout.

Hypophosphatemia
As with other nicotinic acid medicinal products, Pelzont was associated with small decreases in phosphorus levels. Therefore, patients with a risk for hypophosphatemia should be closely followed.

Other information
As with other nicotinic acid medicinal products, patients with a history of jaundice, hepato-biliary disorder or peptic ulcer should be observed closely (see sections 4.2 and 4.3).

Excipient
Pelzont contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Drinking alcohol or hot drinks or eating spicy foods can enhance the effects of flushing and should therefore be avoided around the time of ingestion of Pelzont.

Nicotinic acid
Effects of nicotinic acid on other medicinal products
Antihypertensive therapy: Nicotinic acid may potentiate the effects of ganglionic blocking agents and vasoactive medicinal products such as nitrates, calcium channel blockers, and adrenergic receptor blocking agents, resulting in postural hypotension.

HMG-CoA reductase inhibitors: When simvastatin is combined with nicotinic acid, a modest increase in AUC and C_{max} of simvastatin acid (the active form of simvastatin) was observed, which may be devoid of clinical relevance. The pharmacokinetic interaction of Pelzont with statins has been studied only with simvastatin (see section 4.4).

Effects of other medicinal products on nicotinic acid
Bile acid sequestrants: Because co-administration of bile acid sequestrants may reduce the bioavailability of acidic medicinal products such as nicotinic acid, it is recommended that Pelzont be administered > 1 hour before or > 4 hours after administration of a bile acid sequestrant.

Supplements containing nicotinic acid: Vitamins or other nutritional supplements containing (≥ 50 mg/day) of nicotinic acid (or nicotinamide) have not been studied with Pelzont. Physicians should consider the nicotinic acid intake from vitamins and nutritional supplements when prescribing Pelzont.

Medicinal product /laboratory test interactions: In urine glucose tests, nicotinic acid may also give false-positive reactions with cupric sulfate solution (Benedict's reagent).

Laropiprant
Effects of laropiprant on other medicinal products
Midazolam: Multiple doses of laropiprant 40 mg did not affect the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Therefore, laropiprant is not an inducer or inhibitor of CYP3A4. However, the plasma concentration of a metabolite of midazolam, 1'-hydroxymidazolam, was increased approximately 2-fold with multiple doses of laropiprant. Because 1'-hydroxymidazolam is an active metabolite, the sedative effect of midazolam may be increased and caution should be used when laropiprant is co-administered with midazolam.

Other medicinal products: Co-administration of laropiprant 40 mg with midazolam increased the $AUC_{0-\infty}$ and C_{max} of 1'-hydroxymidazolam, a midazolam metabolite, by 98 % and 59 %, respectively.

1'-hydroxymidazolam is metabolised predominantly by uridine diphosphate-glucuronosyltransferases (UGT) 2B4 and 2B7. Clinical and *in vitro* studies support the conclusion that laropiprant is a mild to moderate inhibitor of UGT2B4/UGT2B7. Very few medicinal products are known to be metabolised predominantly by UGT2B4 or UGT2B7. Caution should be used when Pelzont is co-administered with medicinal products metabolised predominantly by UGT2B4 or UGT2B7, for instance zidovudine.

In interaction studies, laropiprant did not have clinically significant effects on the pharmacokinetics of the following medicinal products: simvastatin, warfarin, oral contraceptives, rosiglitazone and digoxin. Based on these data, laropiprant is not expected to cause interactions with substrates of CYP isozymes 3A4, 2C9, 2C8 and human P-glycoprotein (P-gp). In *in vitro* studies, laropiprant did not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP2E1-mediated reactions.

Clopidogrel: In a clinical study, there was no meaningful effect of laropiprant on the inhibition of ADP-induced platelet aggregation by clopidogrel, but there was a modest increase in the inhibition of collagen-induced platelet aggregation by clopidogrel. This effect is unlikely to be clinically important as laropiprant did not increase bleeding time when co-administered with clopidogrel throughout the dosing interval.

Acetylsalicylic acid: In a clinical study, concomitant administration of laropiprant with acetylsalicylic acid did not have an effect on collagen-induced platelet aggregation or on bleeding time compared to treatment with acetylsalicylic acid alone (see section 5.1).

Acetylsalicylic acid and clopidogrel: In a clinical study in dyslipidaemic patients receiving both acetylsalicylic acid (81 mg) and clopidogrel (75 mg), laropiprant induced transient (4 hours post-dose) inhibition of platelet function *in vivo* (as evaluated by bleeding time and platelet aggregation studies), but had little effect across the dosing interval. Patients receiving Pelzont concomitantly with acetylsalicylic acid and clopidogrel should be closely monitored as recommended in the Summary of Product Characteristics for those medicinal products and should be told that it might take longer than usual to stop bleeding and that they should report any unusual bleeding (site or duration) to their physician.

Effects of other medicinal products on laropiprant
CYP3A4 Inhibitor: Clarithromycin (a potent inhibitor of CYP3A4 and P-gp) did not have a clinically meaningful effect on the pharmacokinetics of laropiprant. Laropiprant is not a substrate of human P-gp, and therefore other inhibitors of CYP3A4 and/or P-gp are also not expected to have a clinically meaningful impact on the pharmacokinetics of laropiprant.

4.6 Fertility, pregnancy and lactation

Pregnancy
Pelzont
There are no data from the combined use of nicotinic acid and laropiprant in pregnant women. The combination has not been tested in reproductive toxicity studies. The potential risk for humans is unknown. Therefore, Pelzont should not be used during pregnancy unless clearly necessary.

Nicotinic acid
There are no adequate data from the use of high dose nicotinic acid in pregnant women. Studies in animals have shown foetal developmental toxicity at high doses of nicotinic acid (see section 5.3).

Laropiprant
There are no data from the use of laropiprant in pregnant women. Studies in animals have shown foetal developmental toxicity at high doses of laropiprant (see section 5.3).

Breast-feeding
Pelzont
No studies in lactating animals have been conducted with Pelzont. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of Pelzont to the woman.

Nicotinic acid
Nicotinic acid is excreted in human breast milk.

Laropiprant
It is unknown whether laropiprant is excreted in human breast milk. Animal studies have shown excretion of laropiprant in milk.

Fertility
Animal studies are insufficient with respect to impairment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines, it should be taken into account that dizziness has been reported (see section 4.8).

4.8 Undesirable effects

In clinical trials, over 5,700 patients received Pelzont alone or with an HMG-CoA reductase inhibitor.

Summary of the safety profile
Flushing is the most common adverse reaction of Pelzont. Flushing is most prominent in the head, neck, and upper torso. In a pool of four active- or placebo-controlled clinical trials (N=4,747, n=2,548 taking Pelzont), flushing was reported in 12.3 % of patients taking Pelzont. In these studies, the percentage of patients taking Pelzont, nicotinic acid (pooled prolonged-release formulations) or pooled placebo/simvastatin who discontinued due to any flushing-related symptom (redness, warmth, itching and tingling) was 7.2 %, 16.6 %, and 0.4 %, respectively.

Tabulated list of adverse reactions
The following adverse reactions have been reported during clinical studies and/or post-marketing use with Pelzont (with or without a statin).

The frequencies of adverse reactions are ranked according to the following: 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).

System organ class	**Adverse reaction**
Infections and infestations	*Rare*: rhinitis
Immune system disorders	*Uncommon*: hypersensitivity reaction (see below) *Rare*: angio-oedema; type I hypersensitivity *Not known*: anaphylactic shock
Metabolism and nutrition disorders	*Uncommon*: gout *Rare*: impaired glucose tolerance
Psychiatric disorders	*Uncommon*: insomnia *Rare*: anxiety
Nervous system disorders	*Common*: headache; paraesthesia *Uncommon*: dizziness *Rare*: migraine; syncope
Cardiac disorders	*Uncommon*: palpitations *Rare*: atrial fibrillation and other cardiac arrhythmias; tachycardia

System organ class	Adverse reaction
Vascular disorders	*Very common*: flushing *Uncommon*: hypotension *Rare*: orthostatic hypotension
Respiratory, thoracic, and mediastinal disorders	*Uncommon*: dyspnoea
Gastrointestinal disorders	*Common*: abdominal pain; diarrhoea; dyspepsia; nausea; vomiting *Rare*: mouth oedema; eructation; peptic ulcer
Hepatobiliary disorders	*Not known*: jaundice
Skin and subcutaneous tissue disorders	*Common:* erythema; pruritus; rash; urticaria *Uncommon*: dry skin; macular rash *Rare*: acanthosis nigricans; hyperpigmentation; sweating (night or cold sweat) *Not known*: vesicular or vesiculobullous rash
Musculoskeletal and connective tissue disorders	*Uncommon*: myalgia *Rare*: muscular weakness
General disorders and administration site conditions	*Common*: feeling hot *Uncommon*: chills; pain; peripheral oedema *Rare*: asthaenia; face oedema; generalised oedema
Investigations	*Common*: elevations in ALT and/or AST (consecutive, ≥ 3 X ULN), fasting glucose (see below) *Uncommon*: elevations in CK (≥ 10 X ULN), LDH, uric acid (see below) *Rare:* elevations in total bilirubin, amylase; reductions in phosphorus and platelet counts (see below)

Hypersensitivity reactions
An apparent hypersensitivity reaction has been reported (< 1 %). This is characterised by multiple symptoms that may include: angio-oedema, pruritus, erythema, paraesthesia, loss of consciousness, vomiting, urticaria, flushing, dyspnoea, nausea, incontinence of urine and stool, cold sweats, shivering, chills, increased blood pressure, lip swelling, burning sensation, drug eruption, arthralgia, leg swelling, and tachycardia.

Investigations
Marked and persistent increases of serum transaminases have been reported infrequently (see section 4.4). In controlled clinical studies, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was 1.0 % for patients treated with Pelzont with or without a statin. These elevations were generally asymptomatic and returned to baseline after discontinuation of therapy or with continued treatment.

Clinically important elevations of CK (≥ 10 X ULN) were seen in 0.3 % of the patients treated with Pelzont with or without a statin (see section 4.4).

Other abnormal laboratory values reported were elevations in LDH, fasting glucose, uric acid, total bilirubin, and amylase, and reductions in phosphorus and platelet counts (see section 4.4).

As with other nicotinic acid medicinal products, elevations in fasting glucose (a median increase of approximately 4 mg/dL), and uric acid (mean change from baseline of +14.7 %), and reductions in platelet counts (a mean change from baseline of -14.0 %) were reported in controlled clinical studies with Pelzont (2,000 mg/40 mg) (see section 4.4). In diabetic patients a median increase in HbA1c of 0.2 % was observed (where modification of hypoglycaemic therapy was allowed).

Additional adverse reactions reported with other nicotinic acid medical products
Additional adverse reactions that have been reported with other nicotinic acid medicinal products (with or without a statin) in post-marketing use or in clinical trials include the following:

Eye disorders: Cystoid macular oedema, toxic amblyopia.

4.9 Overdose

Pelzont
In the event of an overdose, it is reasonable to employ the usual symptomatic and supportive measures. Cases of overdose have been reported; the maximum dose of Pelzont taken was 5,000 mg/100 mg. All patients recovered without sequelae. The most commonly reported adverse reactions from the subjects who received this higher dose were consistent with a high dose of nicotinic acid and included: flushing, headache, pruritus, nausea, dizziness, vomiting, diarrhoea, epigastric and abdominal pain/discomfort, and back pain. Laboratory abnormalities included increased amylase and lipase, decreased haematocrit and occult blood in the stool.

Nicotinic acid
For an overdose of nicotinic acid, supportive measures should be employed.

Laropiprant
During controlled clinical trials in healthy subjects, single doses of up to 900 mg laropiprant and multiple doses up to 450 mg once daily for 10 days were generally well tolerated. There is no experience with doses of laropiprant above 900 mg in humans. Prolongation of collagen-induced platelet aggregation was observed in subjects taking multiple doses of 300 mg or greater (see section 5.1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, nicotinic acid and derivatives, ATC code: C10AD52.

Pelzont contains nicotinic acid, which at therapeutic doses is a lipid-modifying agent, and laropiprant, a potent, selective antagonist of the prostaglandin D_2 (PGD_2) receptor subtype 1 (DP_1). Nicotinic acid lowers the levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B, the major LDL protein), triglycerides (TG), and lipoprotein(a) (Lp(a), a modified LDL particle) and elevates the levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apo A-I, the major protein component of HDL). Laropiprant suppresses PGD_2 mediated flushing associated with administration of nicotinic acid. Laropiprant has no effect on lipid levels nor does it interfere with the effects of nicotinic acid on lipids.

Nicotinic acid
Mechanism of action
The mechanisms by which nicotinic acid modifies the plasma lipid profile are not fully understood. Nicotinic acid inhibits release of free fatty acids (FFA) from adipose tissue, which may contribute to the reduced plasma LDL-C, TC, VLDL-C, apo B, TG, and Lp(a), as well as elevated HDL-C, and apo A-I, all of which are associated with lower cardiovascular risk. Additional explanations that do not invoke plasma FFA reduction as the central driver of lipid profile modification include nicotinic acid-mediated inhibition of *de novo* lipogenesis or esterification of fatty acids into TG in the liver.

Pharmacodynamic effects
Nicotinic acid causes a relative shift in the distribution of LDL subclasses from small, dense (most atherogenic) LDL particles to larger LDL particles. Nicotinic acid also elevates the HDL_2 subfraction to a greater extent than the HDL_3 subfraction, thereby increasing the HDL_2:HDL_3 ratio, which is associated with decreased cardiovascular disease risk. HDL is hypothesised to participate in the transport of cholesterol from tissues back to the liver, to suppress vascular inflammation associated with atherosclerosis, and to have anti-oxidative and anti-thrombotic effects.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG levels are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD).

Treatment with nicotinic acid reduces the risk of death and cardiovascular events, and slows progression or promotes regression of atherosclerotic lesions. The Coronary Drug Project, a five year study completed in 1975, showed that nicotinic acid had a statistically significant benefit in decreasing nonfatal, recurrent myocardial infarctions (MI) in men 30 to 64 years old with a history of MI. Though total mortality was similar in the two groups at five years, in a fifteen-year cumulative follow-up there were 11 % fewer deaths in the nicotinic acid group compared to the placebo cohort.

Laropiprant

Mechanism of action

Nicotinic acid-induced flushing is mediated primarily by release of prostaglandin D_2 (PGD_2) in the skin. Genetic and pharmacologic studies in animal models have provided evidence that PGD_2, acting through DP_1, one of the two receptors for PGD_2, plays a key role in nicotinic acid-induced flushing. Laropiprant is a potent and selective antagonist of DP_1. Laropiprant is not expected to inhibit the production of prostaglandins.

Pharmacodynamic effects

Laropiprant has been shown to be effective in reducing flushing symptoms induced by nicotinic acid. The reduction in flushing symptoms (assessed by patient questionnaires) was correlated with a reduction in nicotinic acid-induced vasodilatation (assessed by measurements of skin blood flow). In healthy subjects receiving Pelzont, pretreatment with acetylsalicylic acid 325 mg had no additional beneficial effects in reducing nicotinic acid-induced flushing symptoms compared to Pelzont alone (see section 4.8).

Laropiprant also has affinity for the thromboxane A_2 receptor (TP) (although it is substantially less potent at TP as compared to DP_1). TP plays a role in platelet function; however, therapeutic doses of laropiprant had no clinically relevant effect on bleeding time and collagen-induced platelet aggregation (see section 4.5).

Clinical studies

Effect on lipids

Pelzont was consistently efficacious across all prespecified patient subpopulations defined by race, gender, baseline LDL-C, HDL-C and TG levels, age and diabetes status.

In a multicentre, double-blind, 24-week placebo-controlled study, patients taking Pelzont (2,000 mg/40 mg) with or without a statin, when compared to placebo, had significantly decreased LDL-C (-18.9 % vs. -0.5 %), TG (-21.7 % vs. 3.6 %), LDL-C:HDL-C (-28.9 % vs. 2.3 %), non-HDL-C (-19.0 % vs. 0.8 %), apo B (-16.4 % vs. 2.5 %), TC (-9.2 % vs. -0.6 %), Lp(a) (-17.6 % vs. 1.1 %), and TC:HDL-C (-21.2 % vs. 1.9 %) and also had significantly increased HDL-C (18.8 % vs. -1.2 %), and apo A-I (11.2 % vs. 4.3 %) as measured by percent change from baseline. In general, the between-group treatment effects on all lipid parameters were consistent across all patient subgroups examined. Patients receiving Pelzont, nicotinic acid (prolonged-released formulation), or placebo were also taking statins (29 % atorvastatin [5-80 mg], 54 % simvastatin [10-80 mg], 17 % other statins [2.5-180 mg] (pravastatin, fluvastatin, rosuvastatin, lovastatin)), of which 9 % were also taking ezetimibe [10 mg]. The effect on lipids was similar whether Pelzont was given as monotherapy or was added to ongoing statin therapy with or without ezetimibe.

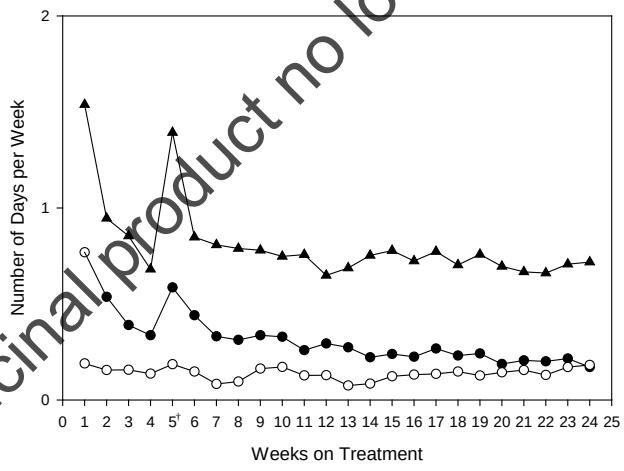
The placebo-adjusted LDL-C, HDL-C and TG responses appeared greater among women compared to men and appeared greater among elderly patients (≥ 65 years) compared to younger patients (< 65 years).

In a multicentre, double-blind, 12-week factorial study, Pelzont 1,000 mg/20 mg co-administered with simvastatin, when compared with simvastatin alone or Pelzont 1,000 mg/20 mg alone, for 4 weeks, significantly lowered LDL-C (-44.2 %, -37.4 %, -8.2 % respectively), TG (-25.8 %, -15.7 %, -18.7 % respectively), TC (-27.9 %, -25.8 %, -4.9 % respectively) and significantly increased HDL-C (19.2 %, 4.2 %, 12.5 % respectively). Pelzont (2000 mg/40 mg) co-administered with simvastatin when compared with simvastatin alone or Pelzont (2000 mg/40 mg) alone for 12 weeks, significantly lowered LDL-C (-47.9 %, -37.0 %, -17.0 % respectively), TG (-33.3 %, -14.7 %, -21.6 % respectively), apo B (-41.0 %, -28.8 %, -17.1 % respectively), and TC (-29.6 %, -24.9 %, -9.1 % respectively), as well as LDL-C:HDL-C (-57.1 %, -39.8 %, -31.2 % respectively), non-HDL-C (-45.8 %, -33.4 %, -18.1 % respectively), and TC:HDL-C (-43.0 %, -28.0 %, -24.9 % respectively), and significantly increased HDL-C (27.5 %, 6.0 %, 23.4 % respectively). Further analysis showed Pelzont (2000 mg/40 mg) co-administered with simvastatin when compared with simvastatin alone significantly increased apo A-I (8.6 %, 2.3 % respectively) and significantly decreased Lp(a) (-19.8 %, 0.0 % respectively). Efficacy and safety of Pelzont in combination with simvastatin > 40 mg were not included in this study.

Flushing

In three large clinical trials measuring patient-reported flushing symptoms, patients taking Pelzont experienced less flushing than those taking nicotinic acid (prolonged-release formulations). In patients continuing in the first study (24 weeks), the frequency of moderate or greater flushing in patients treated with Pelzont declined and approached that of patients receiving placebo (see Figure 1), whereas in patients treated with nicotinic acid (prolonged-release formulation) the flushing frequency remained constant (after Week 6).

Figure 1. Average number of days per week with moderate or greater* flushing symptoms across weeks 1-24



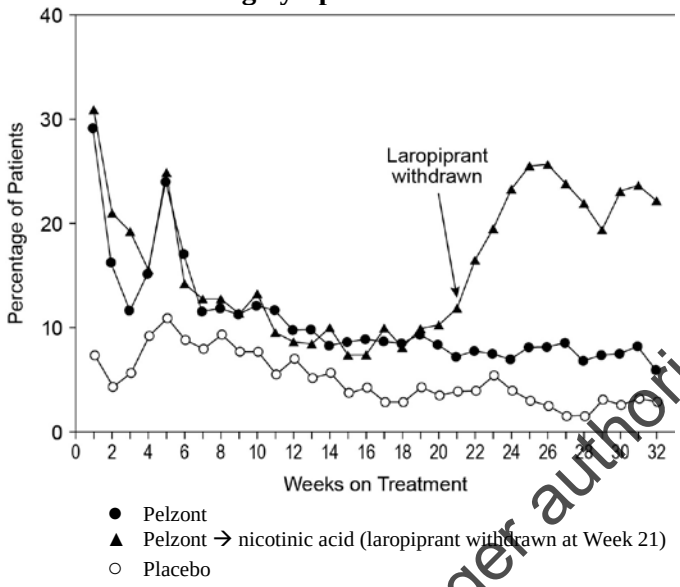
●Pelzont (1000 mg/20 mg to 2000 mg/40 mg at week 5)
▲Nicotinic acid (prolonged-release 1000 mg to 2000 mg at week 5)
○Placebo
*Includes patients with moderate, severe, or extreme flushing symptoms
†Dose advancement at Week 5

In the second study (16 weeks) where acetylsalicylic acid was allowed, patients taking Pelzont experienced significantly fewer days per week with moderate or greater flushing compared to nicotinic acid (prolonged-release formulation taken as a 12-week multi-step 500 mg to 2,000 mg titration) ($p < 0.001$).

A multicenter, randomized, double-blind, placebo-controlled 32-week study to assess the effects of withdrawal of laropiprant showed that dyslipidaemic patients in whom laropiprant was withdrawn after 20 weeks on Pelzont experienced significantly more flushing than patients who continued taking

Pelzont in terms of number of days per week with moderate or greater flushing, p< 0.001, Figure 2. The incidence and frequency of moderate or greater flushing in patients treated with Pelzont for the duration of the study decreased.

Figure 2
Percentage of Patients with Moderate or Greater Flushing Symptoms Across Weeks 1-32



Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Pelzont in all subsets of the paediatric population in homozygous familial hypercholesterolaemia (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Pelzont in paediatric patients from 7-18 years old in heterozygous familial hypercholesterolaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Nicotinic acid
Following a 2,000 mg dose of nicotinic acid administered orally as two modified-release tablets of nicotinic acid/laropiprant with food, nicotinic acid was absorbed with a median time to peak plasma concentration (T_{max}) of 4 hours, a mean area under the plasma concentration-time curve ($AUC_{0\text{-}last}$) of approximately 58.0 μM·hr and a mean peak plasma concentration (C_{max}) of approximately 20.2 μM. Bioavailability with or without food is at least 72 % based on the recovery of the nicotinic acid dose in the urine. The oral bioavailability of nicotinic acid is not altered when it is taken with a high-fat meal.

Laropiprant
Following a 40 mg dose of laropiprant administered orally as two modified-release tablets of nicotinic acid/laropiprant with food, laropiprant is rapidly absorbed with a median T_{max} of 1 hour, a mean $AUC_{0\text{-}\infty}$ of approximately 13 μM·hr, and a mean C_{max} of approximately 1.6 μM. The rate and extent of absorption are not altered with a high-fat meal. The pharmacokinetics of laropiprant are linear, displaying approximately dose-proportional increases in AUC and C_{max} and no evidence of time-dependent clearance.

The mean absolute bioavailability of laropiprant is approximately 71 % following a 40 mg dose when administered as two modified-release tablets of nicotinic acid/laropiprant after an overnight fast.

Distribution

Nicotinic acid

Nicotinic acid is less than 20 % bound to serum proteins.

Laropiprant

The mean volume of distribution at steady state following a single 40 mg intravenous dose of laropiprant to healthy subjects is approximately 70 litres. Laropiprant is highly bound (> 99 %) to plasma proteins, and its binding is independent of concentration. Laropiprant crosses the placenta in rats and rabbits.

Biotransformation

Nicotinic acid

Nicotinic acid undergoes extensive first-pass metabolism through two pathways that are dose and dose-rate dependent. The first pathway results in the formation of nicotinamide adenine dinucleotide (NAD) and nicotinamide. In humans, nicotinamide is further predominantly metabolised to N-methylnicotinamide (MNA) and to N-methyl-2-pyridone-5-carboxamide (2PY). In the second pathway, glycine is conjugated with nicotinic acid to form nicotinuric acid (NUA). With low doses of nicotinic acid or lower rates of absorption, the first pathway predominates. At higher doses or higher rates of absorption, the NAD pathway is saturable, and an increasing fraction of the oral dose reaches the bloodstream unchanged as nicotinic acid. The glycine conjugation pathway is not saturated across the clinically relevant dose range, based on the dose-proportional increase in the plasma concentrations of NUA from 1,000 mg to 2,000 mg.

In *in vitro* studies, nicotinic acid and its metabolites did not inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4-mediated reactions or UGT1A1-mediated 3-glucuronidation of estradiol.

Laropiprant

Laropiprant is metabolised primarily via acyl glucuronidation, with a smaller component of oxidative metabolism, followed by excretion of the glucuronide into faeces (via bile) and urine. Laropiprant and its acyl glucuronide conjugate are the major circulating components in human plasma. *In vitro* studies have shown that the acyl glucuronide conjugate of laropiprant had at least a 65-fold reduced affinity for DP_1 as compared to laropiprant; thus, it is not expected to contribute to the overall DP_1 activity of laropiprant. The major component (78 % of radioactivity) in faeces is laropiprant (comprising unabsorbed active substance and/or hydrolysed glucuronic acid conjugate). In urine, the primary component is the acyl glucuronide conjugate (64 % of radioactivity) with smaller contributions from the parent compound (5 %). The oxidative metabolism of laropiprant is catalysed primarily by CYP3A4, whereas several UGT isoforms (1A1, 1A3, 1A9 and 2B7) catalysed the acyl glucuronidation.

Elimination

Nicotinic acid

Nicotinic acid is predominantly excreted in the urine as metabolites.

Laropiprant

Laropiprant is eliminated primarily via acyl glucuronidation, followed by excretion of the glucuronide in faeces (via bile) and urine. Following oral administration of ^{14}C-laropiprant in humans, approximately 68 % of the dose was recovered in faeces (primarily as parent compound, comprising unabsorbed active substance and/or hydrolysed glucuronic acid conjugate) and 22 % was recovered in urine (primarily as metabolites). The majority of the dose was excreted within 96 hours. The apparent terminal half-life ($t_{1/2}$) following a 40 mg dose of laropiprant administered as two modified-release tablets of nicotinic acid/laropiprant with food was approximately 17 hours. Pharmacokinetic steady state is achieved within 2 days of once-daily dosing of laropiprant, with minimal accumulation in AUC (approximately 1.3-fold) and C_{max} (approximately 1.1-fold).

Characteristics in patients

Renal insufficiency

Pelzont: Use in patients with renal insufficiency has not been studied.

Nicotinic acid: see section 4.4.

Laropiprant: Administration of laropiprant 40 mg in non-dialysed patients with severe renal insufficiency resulted in no clinically meaningful change in the AUC and C_{max} of laropiprant, compared to healthy control subjects. As no effect was observed in severe renal insufficiency, no effect is expected in patients with mild and moderate renal insufficiency; however, the effects of end-stage renal failure and dialysis on laropiprant pharmacokinetics cannot be inferred from this study.

Hepatic insufficiency

Pelzont: Use in patients with hepatic insufficiency has not been studied.

Nicotinic acid: see sections 4.3 and 4.4.

Laropiprant: Consistent with the characteristics of a medicinal product that is primarily cleared by metabolism, moderate hepatic disease has a significant impact on laropiprant pharmacokinetics, with an increase in AUC and C_{max} of approximately 2.8- and 2.2-fold respectively.

Gender

Nicotinic acid: No dose adjustment is necessary based on gender. Gender has no clinically meaningful effect on pharmacokinetics of nicotinic acid (prolonged-release formulation). There is no difference in the oral bioavailability of nicotinic acid in men and women receiving Pelzont. Women have a modest increase in plasma concentrations of nicotinuric acid and nicotinic acid compared to men.

Laropiprant: No dose adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of laropiprant.

Elderly

Nicotinic acid: There is no pharmacokinetic data in the elderly (≥ 65 years). Age has no clinically meaningful effect on pharmacokinetics of nicotinic acid (prolonged-release formulation) based on a composite analysis of subjects ages 18-65 years. There is no change in the oral bioavailability of nicotinic acid with age.

Laropiprant: No dose adjustment is necessary in the elderly. Age had no clinically meaningful effect on the pharmacokinetics of laropiprant.

Paediatric population

Pelzont: No studies have been performed in paediatric patients.

Race

Nicotinic acid: No dose adjustment is necessary based on race. Race has no clinically meaningful effect on the pharmacokinetics of nicotinic acid (prolonged-release formulation) based on pharmacokinetic data including subjects of Hispanic, White, Black, and Native American racial groups. Caution should be used when treating Chinese patients with Pelzont co-administered with simvastatin or ezetimibe/simvastatin (particularly simvastatin doses of 40 mg or higher). (See section 4.4).

Laropiprant: No dose adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of laropiprant based on a composite analysis of pharmacokinetic data including subjects of White, Hispanic, Black, Asian, and Native American racial groups.

5.3 Preclinical safety data

Pelzont
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to human use.

The safety of concomitant administration of nicotinic acid and laropiprant was assessed in dogs and rats. Toxicologic findings in these co-administration studies were consistent with those seen with nicotinic acid and laropiprant administered individually.

Nicotinic acid
Degeneration in the stomach and hepatocyte vacuolation were observed in rats following 6 months of dosing at systemic exposure values at least 179 times the human exposure based on the AUC of the recommended daily human dose. Retinopathy and/or corneal lesions were observed in dogs following 6 months of dosing at systemic exposure values at least 240 times the human exposure based on the AUC of the recommended daily human dose.

Nicotinic acid was not carcinogenic in mice when administered for the duration of their life. Mice in this study received approximately 9 to 13 times a human nicotinic acid dose of 2,000 mg/day as determined on a mg/m^2 basis. Nicotinic acid showed no mutagenic effects in the *in vitro* assays.

No nicotinic acid-related adverse effects on fertility were observed in male and female rats up to exposure levels approximately 391 times the human AUC of nicotinic acid based on the AUC of the recommended daily human dose.

Nicotinic acid was not teratogenic in rats and rabbits up to exposure levels approximately 253 and 104 times the human AUC of nicotinic acid at the recommended daily human dose, respectively. In rats, foetotoxic effects (significantly decreased foetal body weights associated with a decrease in the number of ossified sacrocaudal vertebrae and an increased incidence of foetuses with sites of incomplete ossification) were noted in the absence of any signs of maternal toxicity at exposure levels approximately 959 times the human AUC of nicotinic acid at the recommended daily human dose. Similar treatment-related changes were observed in rabbit foetuses but in the presence of maternal toxicity at exposure levels approximately 629 times the human AUC of nicotinic acid at the recommended daily human dose.

Laropiprant
Ketonuria and hepatocellular centrilobular hypertrophy were observed in rats in repeated dose toxicity studies for up to 6 months dosing. The hepatocellular centrilobular hypertrophy was consistent with rodent specific enzyme induction. The no-observed-adverse-effect level (NOAEL) was at least 118 times the human exposure based on the AUC of the recommended daily human dose.

Increases in serum alanine aminotransferase (ALT) levels were observed in all dog studies, at systemic exposure levels at least 14 times the human exposure based on the AUC of the recommended daily human dose. No other effects were observed in dog studies with exposures at least 100 times the human exposure based on the AUC of the recommended daily human dose.

Laropiprant was not carcinogenic in 2 year studies in mice and rats at the highest doses tested, which represents at least 218 to 289 times the human exposure based on the AUC of the recommended daily human dose.

Laropiprant was not mutagenic or clastogenic in a series of genetic toxicology studies.

No adverse effects on fertility were observed in male or female rats given laropiprant prior to mating and throughout mating, at systemic exposure levels at least 289 times the human exposure based on the AUC of the recommended daily human dose.

Laropiprant was not teratogenic in rats or in rabbits at systemic exposure levels at least 153 and 438 times the human exposure based on the AUC of the recommended daily human dose. Reproduction toxicity studies showed slight treatment-related decreases in mean maternal weight gain and foetal body weight, slight increases in pup mortality, and increased incidence of supernumerary rib and incomplete ossification of the sternebra in the foetus were observed in rats at systemic exposure levels at least 513 times the human exposure based on the AUC of the recommended daily human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose (E464)
Colloidal anhydrous silica (E551)
Sodium stearyl fumarate
Hydroxypropylcellulose (E463)
Microcrystalline cellulose (E460)
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/Aclar blisters: 2 years.
Aluminium/Aluminium blisters: 18 months.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Opaque PVC/Aclar blister with push-through aluminium lidding containing 14 modified-release tablets. Pack sizes of 14, 28, 56, 84, 98, 168, 196 modified-release tablets, multi-packs containing 196 (2 packs of 98) modified-release tablets and 49 x 1 modified-release tablets in a perforated unit dose blister.

Aluminium/Aluminium blister with push-through lidding containing 7 modified-release tablets. Pack sizes of 14, 28, 56, 168 modified-release tablets and 32 x 1 modified-release tablets in a perforated unit dose blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/460/001
EU/1/08/460/002
EU/1/08/460/003
EU/1/08/460/004
EU/1/08/460/005
EU/1/08/460/006
EU/1/08/460/007
EU/1/08/460/008
EU/1/08/460/009
EU/1/08/460/010
EU/1/08/460/011
EU/1/08/460/012
EU/1/08/460/013
EU/1/08/460/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck, Sharp & Dohme Ltd.
Shotton Lane
Cramlington
Northumberland NE23 3JU
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (for Alu/Alu blister)

1. NAME OF THE MEDICINAL PRODUCT

Pelzont 1,000 mg/20 mg modified-release tablets
Nicotinic acid/laropiprant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release tablet contains 1,000 mg of nicotinic acid and 20 mg of laropiprant.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 modified-release tablets
28 modified-release tablets
56 modified-release tablets
168 modified-release tablets
32 x 1 modified-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/460/009 14 modified-release tablets
EU/1/08/460/010 28 modified-release tablets
EU/1/08/460/011 56 modified-release tablets
EU/1/08/460/013 168 modified-release tablets
EU/1/08/460/014 32 x 1 modified-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pelzont

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (for PVC/Aclar blister)

1. NAME OF THE MEDICINAL PRODUCT

Pelzont 1,000 mg/20 mg modified-release tablets
Nicotinic acid/laropiprant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release tablet contains 1,000 mg of nicotinic acid and 20 mg of laropiprant.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 modified-release tablets
28 modified-release tablets
56 modified-release tablets
84 modified-release tablets
98 modified-release tablets
168 modified-release tablets
196 modified-release tablets
Multi-pack containing 196 (2 packs of 98) modified-release tablets
49 x 1 modified-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/460/001 14 modified-release tablets
EU/1/08/460/002 28 modified-release tablets
EU/1/08/460/003 56 modified-release tablets
EU/1/08/460/004 84 modified-release tablets
EU/1/08/460/005 98 modified-release tablets
EU/1/08/460/006 168 modified-release tablets
EU/1/08/460/007 196 modified-release tablets
EU/1/08/460/008 49 x 1 modified-release tablets
EU/1/08/460/012 196 (2 packs of 98) modified-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pelzont

PARTICULARS TO APPEAR ON THE INTERMEDIATE CARTON

Multi-packs of 196 (2 packs of 98 modified-release tablets) – without blue box (for PVC/Aclar blister)

1. NAME OF THE MEDICINAL PRODUCT

Pelzont 1,000 mg/20 mg modified-release tablets
Nicotinic acid/laropiprant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release tablet contains 1,000 mg of nicotinic acid and 20 mg of laropiprant.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 modified-release tablets. Component of a multi-pack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/460/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Pelzont 1000 mg/20 mg modified-release tablets
Nicotinic acid/laropiprant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Pelzont 1,000 mg/20 mg modified-release tablets
nicotinic acid/laropiprant

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Pelzont is and what it is used for

The name of your medicine is Pelzont. It contains two different active substances:
- nicotinic acid, a lipid modifying medicine, and
- laropiprant, which reduces symptoms of flushing, a common side effect of nicotinic acid.

How Pelzont Works
Pelzont is used in addition to diet
- to lower your 'bad' cholesterol level. It does this by lowering the levels of total cholesterol, LDL cholesterol, fatty substances called triglycerides and apo B (a part of LDL) in the blood;
- to raise levels of 'good' cholesterol (HDL cholesterol) and apo A-I (a part of HDL).

What should I know about cholesterol and triglycerides?
Cholesterol is one of several fats found in your blood. Your total cholesterol is made up mainly of 'bad' (LDL) and 'good' (HDL) cholesterol.

LDL cholesterol is often called 'bad' cholesterol because it can build up in the walls of your arteries and form plaque. Over time, this plaque build-up can lead to a clogging of your arteries. This clogging can slow or block blood flow to vital organs such as the heart and brain. When the blood flow is blocked, the result can be a heart attack or stroke.

HDL cholesterol is often called 'good' cholesterol because it helps keep the 'bad' cholesterol from building up in the arteries and because it protects against heart disease.

Triglycerides are another fat in your blood. They may raise your risk of having heart problems.

In most people, at first there are no signs of cholesterol problems. Your doctor can measure your cholesterol with a simple blood test. Visit your doctor regularly to keep track of your cholesterol and discuss your goals with your doctor.

Pelzont is used in addition to diet and exercise in adult patients with primary hypercholesterolaemia or mixed dyslipidaemia:
- when you cannot control your cholesterol levels with a statin alone (class of cholesterol-lowering medicines working in the liver);

- when you cannot tolerate a statin or when a statin is not recommended for you.

Patients with combined mixed dyslipidaemia have high blood levels of 'bad' LDL cholesterol and triglycerides (a type of fat), and low levels of 'good' HDL cholesterol. Primary hypercholesterolaemia is when the levels of cholesterol in the blood are high. Primary means that the hypercholesterolaemia does not have any identifiable cause.

2. What you need to know before you take Pelzont

Do not take Pelzont if
- you are allergic to nicotinic acid, to laropiprant, or to any of the other ingredients of this medicine (listed in section 6).
- you currently have liver problems.
- you have an ulcer in your stomach.
- you have arterial bleeding.

Do not take Pelzont if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Pelzont.

Warnings and precautions
Tell your doctor about all of your medical conditions. Check with your doctor or pharmacist before and while taking your medicine if:
- you have any allergies.
- you have ever had liver disease, jaundice (a liver disorder causing yellowing of the skin and whites of the eyes), or hepatobiliary (liver and bile duct) disease.
- you have kidney problems.
- you have thyroid problems.
- you drink large amounts of alcohol.
- you or close family members have a hereditary muscle disorder, or you have ever had muscle problems during treatment with cholesterol-lowering medicines called "statins" or fibrates.
- you have unexplained muscle pain, muscle tenderness, or muscle weakness. If you have these symptoms talk to your doctor immediately.
- you have high blood sugar or diabetes.
- you have heart problems.
- you are going to have an operation.
- you have gout.
- you have low levels of phosphorus.
- you are over 70 years old.
- you are taking simvastatin (a statin) or a medicine containing simvastatin and are Chinese.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Pelzont.

Blood tests and monitoring
- See your doctor regularly to check your LDL (bad) and HDL (good) cholesterol levels and your triglyceride level.
- Your doctor should do a blood test before you start taking Pelzont to check how well your liver is working.
- Your doctor may also want you to periodically have blood tests after you start taking Pelzont, to check how well your liver is working and for other side effects.

Children and adolescents
Pelzont has not been studied in children and adolescents who are under 18 years of age. Therefore, Pelzont should not be used in children and adolescents under 18 years of age.

Other medicines and Pelzont
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, vitamins, and herbal supplements.

In particular, tell your doctor or pharmacist if you are taking any of the following:
- medicines used to lower blood pressure.
- medicines used to lower cholesterol called 'bile acid sequestrants', such as colestyramine.
- zidovudine, a medicine used for HIV.
- midazolam, a medicine to make you sleepy before some medical procedures.
- vitamins or supplements that contain nicotinic acid.
- clopidogrel and acetylsalicylic acid (ASA), medicines to help prevent harmful blood clots.
- medicines used to lower cholesterol called 'statins'.

Also tell your doctor if you are taking simvastatin (a statin) or a medicine containing simvastatin and are Chinese.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Pelzont.

Pelzont with food, drink and alcohol
- To lower your chance of flushing, avoid drinking alcohol or hot drinks or eating spicy foods near the time you take your dose of Pelzont.
- It is important to follow the advice given in section 3 **How to take Pelzont**.

Pregnancy and breast-feeding
Pelzont is not recommended in pregnancy unless clearly necessary.
Talk with your doctor before taking Pelzont if:
- You are pregnant or plan to become pregnant. It is not known if Pelzont will harm your unborn baby.
- You are breast-feeding or plan to breast-feed. It is not known if Pelzont will pass into your breast milk. However, nicotinic acid a component of Pelzont does pass into breast milk.

Ask your doctor or pharmacist for advice before taking this medicine. Your doctor will decide if Pelzont is right for you.

Driving and using machines
Some people get dizzy after taking Pelzont. If you get dizzy, you should avoid driving or operating machines after taking Pelzont.

Pelzont contains lactose
Pelzont contains a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Pelzont

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much to take
- You should start by taking one tablet a day.
- After 4 weeks, your doctor may raise your dose to two tablets a day.
- If you are switching from a medicine containing 2,000 mg or more of a prolonged-release nicotinic acid, your doctor can start you with two tablets of Pelzont a day. If you are switching from a medicine with less than 2,000 mg of prolonged-nicotinic acid, you should start by taking one tablet of Pelzont a day. After 4 weeks, your doctor may raise your dose of Pelzont to two

tablets a day.

How to take
- Take Pelzont once a day, in the evening or at bedtime.
- Take Pelzont with food.
- Swallow each tablet whole. In order for your medicine to work as intended, do not split, break, crush, or chew the tablet before you swallow it.
- Avoid drinking alcohol or hot drinks or eating spicy foods near the time you take your dose of Pelzont. This will lower your chance of flushing (redness of the skin, feeling warm, itching, or tingling, particularly in your head, neck, chest and upper back).
- Taking aspirin before you take Pelzont does not reduce your flushing more than taking Pelzont alone. Therefore, taking aspirin to reduce flushing symptoms is not necessary. If you take aspirin for any other reason, continue to follow your doctor's advice.

If you take more Pelzont than you should
- In the event of an overdose, the following side effects were reported:
flushing, headache, pruritus (itching), nausea, dizziness, vomiting, diarrhoea, abdominal pain/discomfort, and back pain.
- If you take more than you should, talk to a doctor or pharmacist straightaway.

If you forget to take Pelzont
- If you miss a dose, do not take an extra dose. Continue with your usual dose the next evening or at bedtime. However, if you do not take Pelzont for 7 or more days in a row, talk to your doctor before restarting Pelzont.

If you stop taking Pelzont
Do not stop taking Pelzont without talking to your doctor. Your cholesterol problem may return.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects of Pelzont are:

Very common (may affect more than 1 in 10 people)
- flushing (which usually includes redness of the skin, feeling warm, itching, or tingling, particularly in the head, neck, chest and upper back). If flushing occurs, symptoms are generally most noticeable at first and usually lessen over time.

Common (may affect up to 1 in 10 people)
- headache
- tingling or numbness of the hands or feet
- abdominal pain
- diarrhoea
- upset stomach or heartburn
- nausea (feeling sick)
- getting sick (vomiting)
- pruritus (itching)
- rash
- hives

Uncommon (may affect up to 1 in 100 people)
- gout

- sleeplessness
- dizziness
- palpitation (feeling your heartbeat)
- low blood pressure
- shortness of breath
- dry skin
- rash with flat, red spots
- muscle pain or tenderness
- chills
- pain
- swelling of the fingers, toes or ankles

In addition, one or more of the following symptoms have been reported as part of an allergic reaction to Pelzont.
- swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (angioedema, which may require treatment right away)
- fainting
- shortness of breath
- loss of control over urine and stool
- cold sweats
- shivering
- chills
- increased blood pressure
- swelling of the lips
- burning sensation
- whole body rash
- joint pain
- swelling of the legs
- rapid heart rate.

Rare (may affect up to 1 in 1000 people)
- runny nose
- decreased glucose (sugar) tolerance
- anxiety
- migraine
- fainting
- rapid or irregular heartbeat
- dizziness upon standing
- belching
- stomach ulcer
- skin disorder with dark velvety plaques called acanthosis nigricans
- patches of darkened skin
- sweating
- muscle weakness
- weakness
- generalised swelling

Not known: frequency cannot be estimated from the available data
Additionally, the following were reported during post-marketing experience with Pelzont and/or other nicotinic acid products (alone and/or with certain other cholesterol-lowering medicines).
- a sudden serious allergic reaction (anaphylactic shock). Symptoms included fainting, shortness of breath, wheezing or trouble breathing, swelling of the face, lips, tongue, itching or hives on the skin. **This condition requires immediate medical attention.**

- eye disorders called toxic amblyopia and cystoid macular oedema which may lead to blurred, decreased, or lost vision
- yellowing of the skin and/or eyes (jaundice)
- blistering rash.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Pelzont

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP.

Do not store above 30°C. Store in the original packaging in order to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pelzont contains
- The active substances are nicotinic acid and laropiprant. Each tablet contains 1000 mg nicotinic acid and 20 mg laropiprant.
- The other ingredients are: hypromellose (E464), colloidal anhydrous silica (E551), sodium stearyl fumarate, hydroxypropylcellulose (E463), microcrystalline cellulose (E460), croscarmellose sodium, lactose monohydrate and magnesium stearate.

The medicine comes as a modified-release tablet. This means one or more active substances are released slowly over a period of time.

What Pelzont looks like and contents of the pack
Each modified-release tablet is a capsule-shaped, white to off-white tablet, with “552” debossed on one side.

Opaque PVC/Aclar blister with push-through aluminium lidding in pack sizes of 14, 28, 56, 84, 98, 168, 196 modified-release tablets, multi-packs containing 196 (2 packs of 98) modified-release tablets and 49 x 1 modified-release tablets in perforated unit dose blister.

Aluminium/Aluminium blister with push-through lidding in pack sizes of 14, 28, 56,
168 modified-release tablets and 32 x 1 modified-release tablets in perforated unit dose blister.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.