1. NAME OF THE MEDICINAL PRODUCT
INEGY® 10 mg/20 mg, 10 mg/40 mg, or 10 mg/80 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg ezetimibe and 20, 40 or 80 mg of simvastatin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.
White to off-white capsule-shaped tablets with code “312”, “313”, or “315” on one side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypercholesterolaemia
INEGY is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:
• patients not appropriately controlled with a statin alone
• patients already treated with a statin and ezetimibe INEGY contains ezetimibe and simvastatin. Simvastatin (20-40 mg) has been shown to reduce the frequency of cardiovascular events (see section 5.1). Studies to demonstrate the efficacy of INEGY or ezetimibe in the prevention of complications of atherosclerosis have not been completed.

Homozygous Familial Hypercholesterolaemia (HoFH)
INEGY is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).

4.2 Posology and method of administration
Hypercholesterolaemia
The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with INEGY.
Route of administration is oral. The dosage range of INEGY is 10/10 mg/day through 10/80 mg/day in the evening. All dosages may not be available in all member states. The typical dose is 10/20 mg/day or 10/40 mg/day given as a single dose in the evening. The 10/80 mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications. The patient’s low-density lipoprotein cholesterol (LDL-C) level, coronary heart disease risk status, and response to current cholesterol-lowering therapy should be considered when starting therapy or adjusting the dose.
The dose of INEGY should be individualised based on the known efficacy of the various dose strengths of INEGY (see section 5.1, Table 1) and the response to the current cholesterol-lowering therapy. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks. INEGY can be administered with or without food.

Homozygous Familial Hypercholesterolaemia
The recommended dosage for patients with homozygous familial hypercholesterolaemia is INEGY 10/40 mg/day or 10/80 mg/day in the evening. INEGY may be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Coadministration with other medicines
Dosing of INEGY should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.
In patients taking amiodarone or verapamil concomitantly with INEGY, the dose of INEGY should not exceed 10/20 mg/day (see sections 4.4 and 4.5).
In patients taking ciclosporin, danazol or lipid-lowering doses (≥1 g/day) of niacin concomitantly with INEGY, the dose of INEGY should not exceed 10/10 mg/day (see sections 4.4 and 4.5).
INEGY contains simvastatin. Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related for simvastatin. In a clinical trial database in which 41,050 patients were treated with simvastatin with 24,747 (approximately 60%) treated for at least 4 years, the incidence of myopathy was approximately 0.02%, 0.08% and 0.53% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (>5 X ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
All patients starting therapy with INEGY, or whose dose of INEGY is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting treatment in the following situations:

- Elderly (age >70 years)
- Renal impairment

4.3 Contraindications
Hypersensitivity to ezetimibe, simvastatin, or to any of the excipients.
Pregnancy and lactation (see section 4.6).
Active liver disease or unexplained persistent elevations in serum transaminases.
Concomitant administration of potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone) (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use
Myopathy/Rhabdomyolysis
In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis.
increased by concomitant use of other fibrates, lipid-lowering doses (≥1 g/day) of niacin or by concomitant use of amiodarone or verapamil with higher doses of INEGY (see sections 4.2 and 4.5). There is also a slight increase in risk when diltiazem is used with INEGY 10 mg/80 mg. The risk of myopathy including rhabdomyolysis may be increased by concomitant administration of fusidic acid with INEGY (see section 4.5).

Consequently, regarding CYP3A4 inhibitors, the use of INEGY concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with INEGY must be suspended during the course of treatment. Moreover, caution should be exercised when combining INEGY with certain other less potent CYP3A4 inhibitors: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and INEGY should be avoided.

The dose of INEGY should not exceed 10/10 mg daily in patients receiving concomitant medication with ciclosporin, danazol or lipid-lowering doses (≥1 g/day) of niacin. The benefits of the combined use of INEGY 10 mg/10 mg daily with ciclosporin, danazol or niacin should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.)

The combined use of INEGY at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

The safety and efficacy of INEGY administered with fibrates have not been studied. There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates (especially gemfibrozil). Therefore, the concomitant use of INEGY with fibrates is not recommended. (See section 4.5.)

Patients on fusidic acid and INEGY should be close-
Excipient
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

Pharmacodynamic interactions
Interactions with lipid-lowering medicinal products that can cause myopathy when given alone.

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration of simvastatin with fibrates and niacin (nicotinic acid) (≥1 g/day). Additionally, there is a pharmacokinetic interaction of simvastatin with gemfibrozil resulting in increased simvastatin plasma levels (see below Pharmacokinetic interactions).

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see section 5.3). Although the relevance of this preclinical finding to humans is unknown, coadministration of INEGY with fibrates is not recommended (see section 4.4).

Pharmacokinetic interactions
Prescribing recommendations for interacting agents are summarised in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).

| Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis |
|-------------------------------------------------------------------------------------------------
<table>
<thead>
<tr>
<th><strong>Interacting agents</strong></th>
<th><strong>Prescribing recommendations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent CYP3A4 inhibitors:</td>
<td>Contraindicated with INEGY</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td></td>
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<tr>
<td>Telithromycin</td>
<td></td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>Not recommended with INEGY</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Do not exceed 10/10 mg INEGY daily</td>
</tr>
<tr>
<td>Danazol</td>
<td></td>
</tr>
<tr>
<td>Niacin (≥1 g/day)</td>
<td></td>
</tr>
</tbody>
</table>
Caution should be exercised when initiating INEGY in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving INEGY and ciclosporin (see section 4.4).

Fibrates: Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5- and 1.7-fold, respectively. Although these increases are not considered clinically significant, coadministration of INEGY with fibrates is not recommended (see section 4.4).

Simvastatin
Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with INEGY must be suspended. Caution should be exercised when combining INEGY with certain other less potent CYP3A4 inhibitors: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.4).

Ciclosporin: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin particularly with higher doses of INEGY (see sections 4.2 and 4.4). Therefore, the dose of INEGY should not exceed 10/10 mg daily in patients receiving concomitant medication with ciclosporin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>Verapamil</th>
<th>Do not exceed 10/20 mg INEGY daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td></td>
<td>Do not exceed 10/40 mg INEGY daily</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td></td>
<td>Patients should be closely monitored. Temporary suspension of INEGY treatment may be considered.</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td></td>
<td>Avoid grapefruit juice when taking INEGY</td>
</tr>
</tbody>
</table>

**Effects of other medicinal products on INEGY**

**Ezetimibe**

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Colestyramine: Concomitant colestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding INEGY to colestyramine may be lessened by this interaction (see section 4.2).

**Ciclosporin:** In a study of eight post-renal transplant patients with creatinine clearance of >50 ml/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15% increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of conadministered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating INEGY in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving INEGY and ciclosporin (see section 4.4).

Grapefruit juice Avoid grapefruit juice when taking INEGY

**Ezetimibe**

**Simvastatin**

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with INEGY must be suspended. Caution should be exercised when combining INEGY with certain other less potent CYP3A4 inhibitors: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.4).

**Ciclosporin:** The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin particularly with higher doses of INEGY (see sections 4.2 and 4.4). Therefore, the dose of INEGY should not exceed 10/10 mg daily in patients receiving concomitant medication with ciclosporin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of
HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.  

_Danazol_: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of INEGY (see section 4.2 and section 4.4).

_Gemfibrozil_: Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway.

_Amiodarone and verapamil_: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

An analysis of the available clinical trials showed an approximately 1% incidence of myopathy in patients receiving simvastatin 40 mg or 80 mg and verapamil. In a pharmacokinetic study, concomitant administration of simvastatin with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of INEGY should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone or verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

_Diltiazem_: An analysis of the available clinical trials showed a 1% incidence of myopathy in patients receiving simvastatin 80 mg and diltiazem. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem with simvastatin caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of INEGY should not exceed 10/40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

_Fusidic acid_: The risk of myopathy including rhabdomyolysis may be increased by concomitant administration of fusidic acid with INEGY (see section 4.4). Specific pathways of fusidic acid metabolism in the liver are not known, however, an interaction between fusidic acid and HMG-CoA reductase inhibitors, which are metabolised by CYP-3A4, can be suspected.

_Grapefruit juice_: Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and administration of simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with INEGY should therefore be avoided.

Effects of INEGY on the pharmacokinetics of other medicinal products

_Ezetimibe_: In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

_Anticoagulants_: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If INEGY is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored. (see section 4.4).

_Simvastatin_: Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.
**Oral anticoagulants:** In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting INEGY and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of INEGY is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

4.6 Pregnancy and lactation

**Pregnancy:**
Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

INEGY
INEGY is contraindicated during pregnancy. No clinical data are available on the use of INEGY during pregnancy. Animal studies on combination therapy have demonstrated reproduction toxicity. (See section 5.3.)

**Simvastatin**
The safety of simvastatin in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, INEGY should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with INEGY should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3.)

**Ezetimibe**
No clinical data are available on the use of ezetimibe during pregnancy.

**Lactation:**
INEGY is contraindicated during lactation. Studies on rats have shown that ezetimibe is excreted into breast milk. It is not known if the active components of INEGY are secreted into human breast milk. (See section 4.3.)

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

4.8 Undesirable effects
INEGY (or coadministration of ezetimibe and simvastatin equivalent to INEGY) has been evaluated for safety in more than 3,800 patients in clinical trials. The frequencies of adverse events are ranked according to the following: Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000),
alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients coadministered ezetimibe and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone). (See section 4.4).

Post-marketing experience
The following additional adverse reactions have been reported in post-marketing experience with ezetimibe. Because these adverse experiences have been identified from spontaneous reports, their true frequencies are not known and cannot be estimated.

**Blood and lymphatic system disorders:**
- thrombocytopaenia

**Nervous system disorders:**
- dizziness

**Gastro-intestinal disorders:**
- nausea, pancreatitis

**Hepato-biliary disorders:**
- hepatitis, cholelithiasis, cholecystitis
- hepatitis/jaundice
- Very rare: hepatic failure

**Skin and subcutaneous tissue disorders:**
- hypersensitivity reactions, including rash, urticaria, anaphylaxis, angio-oedema

**Musculoskeletal, connective tissue disorders:**
- arthralgia, myopathy/rhabdomyolysis (see section 4.4)

**Laboratory values**
increased transaminases; increased CK

**Simvastatin**

**Blood and lymphatic system disorders:**
- dizziness

**Nervous system disorders:**
- rare: anaemia

**Gastro-intestinal disorders:**
- rare: constipation, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

**Hepato-biliary disorders:**
- rare: hepatitis/jaundice
- very rare: hepatic failure
Simvastatin
A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitors in combination with other lipid modifying agents, ATC code: C10BA02
INEGY (ezetimibe/simvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

Mechanism of action:
INEGY
Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. INEGY contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. INEGY reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe
Ezetimibe inhibits the intestinal absorption of cholesterol. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibrin acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.
Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemia-

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

Musculoskeletal, connective tissue and bone disorders:
Rare: myopathy, rhabdomyolysis (see section 4.4), muscle cramps

General disorders and administration site conditions:
Rare: aesthenia

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angio-oedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, red blood cell sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity reaction, pyrexia, flushing, dyspnoea and malaise.

Laboratory Values
Rare: increases in γ-glutamyl transpeptidase, elevated alkaline phosphatase.

4.9 Overdose
INEGY
In the event of an overdose, symptomatic and supportive measures should be employed. Coadministration of ezetimibe (1000 mg/kg) and simvastatin (1000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD_{50} for both species was ezetimibe ≥1000 mg/kg/simvastatin ≥1000 mg/kg.

Ezetimibe
In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.
mic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of $^{[14]}$C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

**Simvastatin**

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active β-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy-3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

**CLINICAL TRIALS**

In controlled clinical studies, INEGY significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C in patients with hypercholesterolaemia.

**Primary Hypercholesterolaemia**

In a double-blind, placebo-controlled, 8-week study, 240 patients with hypercholesterolaemia already receiving simvastatin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going simvastatin therapy. Among simvastatin-treated patients not at LDL-C goal at baseline (~80%), significantly more patients randomised to ezetimibe coadministered with simvastatin achieved their LDL-C goal at study endpoint compared to patients randomised to placebo coadministered with simvastatin, 76% and 21.5%, respectively.

The corresponding LDL-C reductions for ezetimibe or placebo coadministered with simvastatin were also significantly different (27% or 3%, respectively). In addition, ezetimibe coadministered with simvastatin significantly decreased total-C, Apo B, and TG compared with placebo coadministered with simvastatin.

In a multicentre, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks with a mean LDL-C of 2.4 mmol/L (93 mg/dl), were randomised to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to INEGY 10 mg/20 mg. INEGY 10 mg/20 mg was significantly more effective than doubling the dose of simvastatin to 40 mg in further reducing LDL-C (-21% and 0%, respectively), total-C (-14% and -1%, respectively), Apo B (-14% and -2%, respectively), and non-HDL-C (-20% and -2%, respectively) beyond the reductions observed with simvastatin 20 mg. Results for HDL-C and TG between the two treatment groups were not significantly different. Results were not affected by type of thiazolidinedione treatment.

The efficacy of the different dose-strengths of INEGY (10/10 to 10/80 mg/day) was demonstrated in a multicentre, double-blind, placebo-controlled 12-week trial that included all available doses of INEGY and all relevant doses of simvastatin. When patients receiving all doses of INEGY were compared to those receiving all doses of simvastatin, INEGY significantly lowered total-C, LDL-C,
and TG (see Table 1) as well as Apo B (-42% and -29%, respectively), non-HDL-C (-49% and -34%, respectively) and C-reactive protein (-33% and -9%, respectively). The effects of INEGY on HDL-C were similar to the effects seen with simvastatin. Further analysis showed INEGY significantly increased HDL-C compared with placebo.

<table>
<thead>
<tr>
<th>Table 1. Response to INEGY in Patients with Primary Hypercholesterolaemia (Mean % Change from Untreated Baseline)</th>
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<tr>
<td>Treatment (Daily Dose)</td>
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<td>Pooled data (All INEGY doses)c</td>
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<td>Pooled data</td>
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<td>(All simvastatin doses)c</td>
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<td>Simvastatin by dose</td>
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a For triglycerides, median % change from baseline
b Baseline - on no lipid-lowering drug
c INEGY doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, and TG, compared to simvastatin, and significantly increased HDL-C compared to placebo.

In a similarly designed study, results for all lipid parameters were generally consistent. In a pooled analysis of these two studies, the lipid response to INEGY was similar in patients with TG levels greater than or less than 200 mg/dl.

INEGY contains simvastatin. In two large placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (20-40 mg; N=4,444 patients) and the Heart Protection Study (40 mg; N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularisation procedures.

Studies to demonstrate the efficacy of INEGY in the prevention of complications of atherosclerosis have not been completed.

**Homozygous Familial Hypercholesterolaemia (HoFH)**

A double-blind, randomised, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analysed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Coadministered ezetimibe and simvastatin equivalent to INEGY (10 mg/40 mg and 10 mg/80 mg pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients coadministered ezetimibe and simvastatin equivalent to INEGY (10 mg/80 mg, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

### 5.2 Pharmacokinetic properties

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin.

**Absorption:**

**INEGY**

INEGY is bioequivalent to coadministered ezetimibe and simvastatin.

**Ezetimibe**

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be
determined as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as 10-mg tablets.

**Simvastatin**
The availability of the active β-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the β-hydroxyacid and four additional active metabolites.

Relative to the fasting state, the plasma profiles of both active and total inhibitors were not affected when simvastatin was administered immediately before a test meal.

**Distribution:**

**Ezetimibe**
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

**Simvastatin**
Both simvastatin and the β-hydroxyacid are bound to human plasma proteins (95%).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post-dose.

**Biotransformation:**

**Ezetimibe**
Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

**Simvastatin**
Simvastatin is an inactive lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the systemic circulation is low.

Following an intravenous injection of the β-hydroxyacid metabolite, its half-life averaged 1.9 hours.

**Elimination:**

**Ezetimibe**
Following oral administration of ¹⁴C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

**Simvastatin**
Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the faeces within 96 hours. The amount recovered in the faeces represents absorbed drug equivalents excreted in bile as well as unab- sorbed drug. Following an intravenous injection of the β-hydroxyacid metabolite, an average of only 0.3% of the IV dose was excreted in urine as inhibitors.

**Special Populations:**

**Paediatric Patients**
The absorption and metabolism of ezetimibe are
similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population <10 years of age are not available. Clinical experience in paediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH or sitosterolaemia. (See section 4.2.)

Gender
Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.

5.3 Preclinical safety data
INEGY
In coadministration studies with ezetimibe and simvastatin, the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and/or pharmacodynamic interactions following coadministration. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for simvastatin and 1800 times the AUC level for the active metabolite). There was no evidence that coadministration of ezetimibe affected the myotoxic potential of simvastatin.

In dogs coadministered ezetimibe and statins, some liver effects were observed at low exposures (<1 times human AUC). Marked increases in liver enzymes (ALT, AST) in the absence of tissue necrosis were seen. Histopathologic liver findings (bile duct hyperplasia, pigment accumulation, mononuclear cell infiltration and small hepatocytes) were observed in dogs coadministered ezetimibe and simvastatin. These changes did not progress with longer duration of dosing up to 14 months. General recovery of the liver findings was observed upon discontinuation of dosing. These findings were consistent with those described with HMG-CoA inhibitors or attributed to the very low cholesterol levels achieved in the affected dogs.
The coadministration of ezetimibe and simvastatin was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused caudal vertebrae, reduced number of caudal vertebrae) were observed. In a series of *in vivo* and *in vitro* assays, ezetimibe, given alone or coadministered with simvastatin, exhibited no genotoxic potential.

**Ezetimibe**

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Long-term carcinogenicity tests on ezetimibe were negative. Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day.

**Simvastatin**

Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations, and had no effects on fertility, reproductive function or neonatal development.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Butylated hydroxyanisole
- Citric acid monohydrate
- Croscarmellose sodium
- Hypromellose
- Lactose monohydrate
- Magnesium stearate
- Microcrystalline cellulose
- Propyl gallate

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf-life

2 years.

#### 6.4 Special precautions for storage

- Do not store above 30°C.
- Blisters: Store in the original package.
- Bottles: Keep bottles tightly closed.

#### 6.5 Nature and contents of container

**INEGY 10 mg/20 mg, and 10 mg/40 mg**

- White HDPE bottles with foil induction seals, white child-resistant polypropylene closure, and silica gel desiccant, containing 100 tablets.

**INEGY 10/20 mg and 10/40 mg**

- Push-through blisters of opaque polychlorotrifluoroethylene/PVC sealed to vinyl coated aluminum in packs of 90 tablets.

**INEGY 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg**

- Push-through blisters of opaque polychlorotrifluoroethylene/PVC sealed to vinyl coated aluminum in packs of 7, 10, 14, 28, 30, 50, 56, 84, 98, 100, or 300 tablets.

Unit dose push-through blisters of opaque polychlorotrifluoroethylene/PVC sealed to vinyl coated aluminum in packs of 30, 50, 100, or 300 tablets. Not all pack sizes may be marketed.

#### 6.6 Special precautions for disposal

No special requirements.

### 7. MARKETING AUTHORISATION HOLDER

**MSD-SP Ltd**

Hertford Road

Hoddesdon

Hertfordshire

EN11 9BU

United Kingdom
8. MARKETING AUTHORISATION NUMBER
INEGY 10 mg/20 mg Tablets PL 19945/0008
INEGY 10 mg/40 mg Tablets PL 19945/0009
INEGY 10 mg/80 mg Tablets PL 19945/0010

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OF AUTHORISATION
18 November 2004

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April 2008

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Here above is the latest summary of products characteristics submitted to the
Ministry of Health in UAE (August 2008)