Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Inegy 10 mg / 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg ezetimibe and 20 mg of simvastatin.

Excipient: lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product imported from the UK:
White to off-white capsule-shaped tablets with code "312" 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). A beneficial effect of INEGY or ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated.

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 who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see section 4.4 and 5.1). 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 individualized 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. The tablet should not be split.

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 diltiazem or amlodipine concomitantly with INEGY the dose of INEGY should not exceed 10/40 mg/day (see sections 4.4 and 4.5).
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 lipid-lowering doses (≥ 1 g/day) of niacin 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 or danazol concomitantly with INEGY, the dose of INEGY should not exceed 10/10 mg/day (see sections 4.4 and 4.5).

Use in the Elderly
No dosage adjustment is required for elderly patients (see section 5.2).

Use in Children and adolescents
Initiation of treatment must be performed under review of a specialist.
Adolescents ≥10 years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche): The clinical experience in paediatric and adolescent patients (aged 10-17 years old) is limited. The recommended usual starting dose is 10/10 mg once a day in the evening. The recommended dosing range is 10/10 to a maximum of 10/40 mg/day (see sections 4.4 and 5.2).

Children < 10 years: INEGY is not recommended for use in children below age 10 due to insufficient data on safety and efficacy (see section 5.2). The experience in pre-pubertal children is limited**.**

Use in Hepatic Impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6). Treatment with INEGY is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score> 9) liver dysfunction. (See sections 4.4 and 5.2.)

Use in Renal Impairment
No modification of dosage should be necessary in patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance ≤ 30 ml/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously (see section 5.2).

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, fluconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir) 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.

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 10 X 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 41,413 patients were treated with simvastatin, 24,747 (approximately 60 %) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03 %, 0.08 % and 0.61 % at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%. (See sections 4.8 and 5.1.)

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 ≥65 years)
- Female gender
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with any statin-containing product (such as INEGY) should only be initiated with caution. If CK levels are significantly elevated at baseline (>5 X ULN), treatment should not be started.

Whilst on treatment

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with INEGY, 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. If muscular symptoms are severe and cause daily discomfort, even if CK levels are <5 X ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of INEGY or introduction of another statin-containing product may be considered at the lowest dose and with close monitoring.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose of simvastatin (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no assurance that such monitoring will prevent myopathy.

Therapy with INEGY should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of INEGY with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir, nefazodone), as well as ciclosporin, danazol, and gemfibrozil (see section 4.2).

Due to the simvastatin component of INEGY, the risk of myopathy and rhabdomyolysis is also 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). The risk is increased by concomitant use of diltiazem or amlodipine with INEGY 10/80 mg (see sections 4.2 and 4.5). 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, posaconazole, HIV protease inhibitors (e.g. nelfinavir), erythromycin, clarithromycin, telithromycin, and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole posaconazole, 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: fluconazole, 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 or danazol. The benefits of the combined use of INEGY 10 mg/10 mg daily with ciclosporin or danazol 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 lipid-lowering doses (≥ 1 g/day) of niacin should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

Physicians contemplating combined therapy with simvastatin and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or products containing niacin 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.

In an interim analysis of an ongoing clinical outcomes study, an independent safety monitoring committee identified a higher than expected incidence of myopathy in Chinese patients taking simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg and nicotinic acid/laropiprant 2000 mg/40 mg. There was no apparent contribution by ezetimibe to the increased incidence of myopathy. Therefore, caution should be used when treating Chinese patients with INEGY (particularly doses of 10/40 mg or higher) co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic

acid) or products containing niacin. Because the risk of myopathy with statins is dose-related, the use of INEGY 10/80 mg with lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or products containing niacin is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or products containing niacin.

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 combined use of INEGY at doses higher than 10/40 mg daily with diltiazem or amlodipine 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 closely monitored (see section 4.5). Temporary suspension of INEGY treatment may be considered.

Liver Enzymes
In controlled coadministration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥ 3 X ULN) have been observed (see section 4.8).

It is recommended that liver function tests be performed before treatment with INEGY begins and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 X ULN and are persistent, the drug should be discontinued. INEGY should be used with caution in patients who consume substantial quantities of alcohol.

Hepatic Insufficiency
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, INEGY is not recommended (see section 5.2).

Paediatric (10 to 17 Years of Age) Patients
Efficacy and safety of ezetimibe co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys (Tanner stage II or above) and in girls who were at least one year post-menarche.

In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a treatment period > 33 weeks on growth and sexual maturation have not been studied (see sections 4.2 and 4.8)

The safety and efficacy of ezetimibe co-administered with doses simvastatin above 40mg daily have not been studied in paediatric patients 10 to 17 years of age.

Ezetimibe has not been studied in patients younger than 10 years of age or in pre-menarchal girls. (See sections 4.2 and 4.8.)

The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates
The safety and efficacy of ezetimibe administered with fibrates have not been established; therefore, co-administration of INEGY and fibrates is not recommended (see section 4.5).

Ciclosporin
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 4.5).

Anticoagulants
If INEGY is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, INEGY therapy should be discontinued.

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. Additionally, there is a pharmacokinetic interaction of simvastatin with gemfibrozil resulting in increased simvastatin plasma levels (see below *Pharmacokinetic interactions*). Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

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, co-administration of INEGY with fibrates is not recommended (see section 4.4).

Pharmacokinetic interactions

Prescribing recommendations for interacting agents are summarized 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	
Interacting agents	**Prescribing recommendations**
Potent CYP3A4 inhibitors: Itraconazole Ketoconazole Fluconazole, Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone	**Contraindicated with INEGY**
Fibrates	Not recommended with INEGY
Ciclosporin Danazol	Do not exceed 10/10 mg INEGY daily
Amiodarone Verapamil	Do not exceed 10/20 mg INEGY daily

Niacin (≥ 1 g/day)	
Diltiazem Amlodipine	Do not exceed 10/40 mg INEGY daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of INEGY treatment may be considered.
Grapefruit juice	Avoid grapefruit juice when taking INEGY.

Effects of other medicinal products on INEGY

INEGY
Niacin: In a study of 15 healthy adults, concomitant INEGY (10/20 mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22%) and nicotinuric acid (19%) administered as NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5 days following a low-fat breakfast). In the same study, concomitant NIASPAN slightly increased the mean AUCs of ezetimibe (9%), total ezetimibe (26%), simvastatin (20%) and simvastatin acid (35%). These increases are not considered clinically significant. (See sections 4.2 and 4.4).

Drug interaction studies with higher doses of simvastatin have not been investigated.

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.

Cholestyramine: Concomitant cholestyramine 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 cholestyramine 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 Niacin (range 10% decrease to 51% increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co-administered 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).

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, co-administration 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, fluconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), 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, fluconazole, posaconazole, HIV protease inhibitors (e.g. nelfinavir), erythromycin, clarithromycin, telithromycin, and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, fluconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with INEGY must be suspended during the course of treatment. 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 sections 4.2 and 4.4).

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

Amiodarone: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore, the dose of INEGY should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Calcium Channel Blockers

- *Verapamil:* The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). In a pharmacokinetic study, concomitant administration of simvastatin with verapamil resulted in 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 verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

- *Diltiazem:* The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). 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.

- *Amlodipine:* Patients on amlodipine treated concomitantly with simvastatin 80 mg have an increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of INEGY should not exceed 10/40 mg daily in patients receiving concomitant medication with amlodipine, 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 metabolized 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.

Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of

colchicine and simvastatin, however the data are limited.

Rifampicin: Because rifampicin is an inducer of P450 3A4, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) concomitantly with simvastatin should have their plasma cholesterol levels monitored. Appropriate adjustment of INEGY dosage may be warranted to ensure a satisfactory reduction in lipid levels. In a pharmacokinetic study of normal volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93%with concomitant administration of rifampicin.

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 Normalized 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 Fertility, 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 must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with INEGY must 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 co-administration of ezetimibe and simvastatin equivalent to INEGY) has been evaluated for safety in approximately 12,000 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, < 1/100), Rare (≥1/10,000, < 1/1000), Very Rare (< 1/10,000) including isolated reports.

The following adverse reactions were observed in patients treated with INEGY (N=2404) and at a greater incidence than placebo (N=1340).

Adverse reactions with INEGY and at a greater incidence than placebo		
System organ class	**Adverse reactions**	**Frequency**
Investigations	ALT and/or AST increased; blood CK increased	Common
	blood bilirubin increased; blood uric acid increased; gamma-glutamyltransferase increased; international normalised ratio increased; protein urine present; weight decreased	Uncommon
Nervous system disorders	dizziness; headache	Uncommon
Gastrointestinal disorders	abdominal pain; abdominal discomfort; abdominal pain upper; dyspepsia; flatulence; nausea; vomiting	Uncommon
Skin and subcutaneous tissue disorders	pruritus; rash	Uncommon
Musculoskeletal and connective tissue disorders	arthralgia; muscle spasms; muscular weakness; musculoskeletal discomfort; neck pain; pain in extremity	Uncommon
General disorders and administration site condition	asthenia; fatigue; malaise; oedema peripheral	Uncommon
Psychiatric disorders	sleep disorder	Uncommon

The following adverse reactions were observed in patients treated with INEGY (N=9595) and at a greater incidence than statins administered alone (N=8883).

Adverse reactions with INEGY and at a greater incidence than statins		
System organ class	**Adverse reactions**	**Frequency**
Investigations	ALT and/or AST increased	Common
	blood bilirubin increased; blood CK increased; gamma-glutamyltransferase increased	Uncommon
Nervous system disorders	headache; paraesthesia	Uncommon
Gastrointestinal disorders	abdominal distension; diarrhoea; dry mouth; dyspepsia; flatulence; gastrooesophageal reflux disease; vomiting	Uncommon
Skin and subcutaneous tissue disorders	pruritus; rash; urticaria	Uncommon
Musculoskeletal and connective tissue disorders	myalgia	Common
	arthralgia; back pain; muscle spasms; muscular weakness; musculoskeletal pain; pain in extremity	Uncommon
General disorders and administration site condition	asthenia; chest pain; fatigue; oedema peripheral	Uncommon
Psychiatric disorders	insomnia	Uncommon

Paediatric (10 to 17 years of age) Patients
In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥3X ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2%(2 patients) and 0%for elevation of CPK (≥10X ULN). No cases of myopathy were reported.
This trial was not suited for comparison of rare adverse drug reactions.

Laboratory Values
In co-administration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was 1.7% for patients treated with INEGY. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. (See section 4.4.)

Clinically important elevations of CK (≥ 10 X ULN) were seen in 0.2% of the patients treated with INEGY.

Post-marketing Experience
The following additional adverse reactions have been reported in post-marketing use with INEGY or during clinical studies or post-marketing use with one of the individual components.

Blood and lymphatic system disorders: thrombocytopaenia; anaemia

Nervous system disorders: peripheral neuropathy; memory impairment

Respiratory, thoracic and mediastinal disorders: cough; dyspneoa, interstitial lung disease (see section 4.4).

Gastrointestinal disorders: constipation; pancreatitis; gastritis

Skin and subcutaneous tissue disorders: alopecia; erythema multiforme; hypersensitivity reactions, including rash, urticaria, anaphylaxis, angiooedema

Musculoskeletal and connective tissue disorders: muscle cramps; myopathy* (including myositis)/rhabdomyolysis with or without acute renal failure (see section 4.4)

* In a clinical trial, myopathy occurred commonly in patients treated with simvastatin 80 mg/day compared to patients treated with 20 mg/day (1.0 % vs 0.02 %, respectively).

Metabolism and nutrition disorders: decreased appetite

Vascular disorders: hot flush; hypertension

General disorders and administration site conditions: pain

Hepato-biliary disorders: hepatitis/jaundice; hepatic failure; cholelithiasis; cholecystitis

Reproductive system and breast disorders: *erectile dysfunction*

Psychiatric disorders: depression, insomnia

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, thrombocytopaenia, eosinophilia, red blood cell sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity reaction, pyrexia, flushing, dyspnoea and malaise.

Laboratory Values: elevated alkaline phosphatase; liver function test abnormal

The following adverse events have been reported with some statins:
- sleep disturbances, including nightmares
- memory loss
- sexual dysfunction

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.

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], fibric 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 hypercholesterolaemic 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 hydrolyzed 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 catabolized 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 coa-dministered with simvastatin achieved their LDL-C goal at study endpoint compared to patients randomised to placebo co-administered with simvastatin, 76% and 21.5%, respectively.

The corresponding LDL-C reductions for ezetimibe or placebo co-administered with simvastatin were also significantly different (27% or 3%, respectively). In addition, ezetimibe co-administered with simvastatin significantly decreased total-C, Apo B, and TG compared with placebo co-administered 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 co-administered 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 multicenter, 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 1
Response to INEGY in Patients with Primary Hypercholesterolaemia
(Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	HDL-C	TG[a]
Pooled data (All INEGY doses)[c]	353	-38	-53	+8	-28
Pooled data (All simvastatin doses)[c]	349	-26	-38	+8	-15
Ezetimibe10 mg	92	-14	-20	+7	-13
Placebo	93	+2	+3	+2	-2
INEGY by dose					
10/10	87	-32	-46	+9	-21
10/20	86	-37	-51	+8	-31
10/40	89	-39	-55	+9	-32
10/80	91	-43	-61	+6	-28
Simvastatin by dose					
10 mg	81	-21	-31	+5	-4
20 mg	90	-24	-35	+6	-14
40 mg	91	-29	-42	+8	-19
80 mg	87	-32	-46	+11	-26

[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.

In a multicenter, double-blind, controlled clinical study (ENHANCE), 720 patients with heterozygous familial hypercholesterolemia were randomized to receive ezetimibe 10 mg in combination with simvastatin 80 mg (n = 357) or simvastatin 80 mg (n = 363) for 2 years. The primary objective of the study was to investigate the effect of the ezetimibe/simvastatin combination therapy on carotid artery intima-media thickness (IMT) compared to simvastatin monotherapy. The impact of this surrogate marker on cardiovascular morbidity and mortality is still not demonstrated.

The primary endpoint, the change in the mean IMT of all six carotid segments, did not differ significantly (p= 0.29) between the two treatment groups as measured by B-mode ultrasound. With ezetimibe 10 mg in combination with simvastatin 80 mg or simvastatin 80 mg alone, intimamedial thickening increased by 0.0111 mm and 0.0058 mm, respectively, over the study's 2 year duration (baseline mean carotid IMT 0.68 mm and 0.69 mm respectively.

Ezetimibe 10 mg in combination with simvastatin 80 mg lowered LDL-C, total-C, Apo B, and TG significantly more than simvastatin 80 mg. The percent increase in HDL-C was similar for the two treatment groups. The adverse reactions reported for ezetimibe 10 mg in combination with simvastatin 80 mg were consistent with its known safety profile.

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 revascularization procedures.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with simvastatin 80 mg versus 20 mg (median follow-up 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularization procedure, non-fatal or fatal stroke, or peripheral revascularization procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; simvastatin 20 mg (n = 1553; 25.7 %) vs. simvastatin 80 mg (n = 1477; 24.5 %); RR 0.94, 95 % CI: 0.88 to 1.01. The absolute difference in LDL-C between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0 % for patients on simvastatin 80 mg compared with 0.02 % for patients on 20 mg. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1 %.
A beneficial effect of INEGY or ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated.

Clinical Studies in Paediatric Patients (10 to 17 years of age)
In a multicentre, double-blind, controlled study, 142 boys (Tanner stage II and above) and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years) with heterozygous familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 4.1 and 10.4 mmol/l were randomised to either ezetimibe 10 mg co-administered with simvastatin (10, 20 or 40 mg) or simvastatin (10, 20 or 40 mg) alone for 6 weeks, co-administered ezetimibe and 40 mg simvastatin or 40 mg simvastatin alone for the next 27 weeks, and open-label co-administered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

At Week 6, ezetimibe co-administered with simvastatin (all doses) significantly reduced total-C (38 % vs 26 %), LDL-C (49 %vs 34 %), Apo B (39 %vs 27 %), and non-HDL-C (47 %vs 33 %) compared to simvastatin (all doses) alone. Results for the two treatment groups were similar for TG and HDL-C (-17 % vs -12 %and +7 %vs +6 %, respectively). At Week 33, results were consistent with those at Week 6 and significantly more patients receiving ezetimibe and 40 mg simvastatin (62 %) attained the NCEP AAP ideal goal (< 2.8 mmol/L [110 mg/dL]) for LDL-C

compared to those receiving 40 mg simvastatin (25 %). At Week 53, the end of the open label extension, the effects on lipid parameters were maintained.

The safety and efficacy of ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

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. Co-administered 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 co-administered 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.

Aortic Stenosis
The Simvastatin and Ezetimibe for the Treatment of Aortic Stenosis (SEAS) study was a multi-center, double-blind, placebo-controlled study with a median duration of 4.4 years conducted in 1873 patients with asymptomatic aortic stenosis (AS), documented by Doppler-measured aortic peak flow velocity within the range of 2.5 to 4.0 m/s. Only patients who were considered not to require statin treatment for purposes of reducing atherosclerotic cardiovascular disease risk were enrolled. Patients were randomized 1:1 to receive placebo or co-administered ezetimibe 10 mg and simvastatin 40 mg daily.

The primary endpoint was the composite of major cardiovascular events (MCE) consisting of cardiovascular death, aortic valve replacement (AVR) surgery, congestive heart failure (CHF) as a result of progression of AS, nonfatal myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), hospitalization for unstable angina, and non-hemorrhagic stroke. The key secondary endpoints were composites of subsets of the primary endpoint event categories.

Compared to placebo, ezetimibe/simvastatin 10/40 mg did not significantly reduce the risk of MCE.
The primary outcome occurred in 333 patients (35.3%) in the ezetimibe / simvastatin group and in 355 patients (38.2%) in the placebo group (hazard ratio in the ezetimibe / simvastatin group, 0.96; 95% confidence interval, 0.83 to 1.12; p = 0.59). Aortic valve replacement was performed in 267 patients (28.3%) in the ezetimibe / simvastatin group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; p = 0.97). Fewer patients had ischemic cardiovascular events in the ezetimibe / simvastatin group (n=148) than in the placebo group (n=187) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; p = 0.02), mainly because of the smaller number of patients who underwent coronary artery bypass grafting.

Cancer occurred more frequently in the ezetimibe / simvastatin group (105 versus 70, p = 0.01). The clinical relevance of this observation is uncertain. In a meta-analysis including interim results from two large, long-term, ongoing studies with ezetimibe / simvastatin (n=10,319 actively treated, 10,298 control treated; patient-years = 18,246 actively treated, 18,255 control treated) there was not an increased rate of cancer (313 active treatment, 326 control; risk ratio, 0.96; 95% confidence interval, 0.82 to 1.12; p = 0.61).

5.2 Pharmacokinetic properties

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.

Absorption:
INEGY
INEGY is bioequivalent to co-administered 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 (C_{max}) 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 ^{14}C-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 unabsorbed 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 (includes patients with HoFH, HeFH or sitosterolaemia.. (See section 4.2.)

Geriatric Patients
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and younger subjects treated with ezetimibe. (See section 4.2.)
Hepatic Insufficiency
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score> 9) hepatic insufficiency, ezetimibe is not recommended in these patients (see sections 4.2 and 4.4).

Renal Insufficiency
Ezetimibe
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 ml/min), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). (See section 4.2.)

An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Simvastatin
In a study of patients with severe renal insufficiency (creatinine clearance < 30 ml/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

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

The shelf-life expiry date of this product shall be the date shown on the blister strip and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Push-through blisters of opaque polychlorotrifluoroethylene /PVC sealed to vinyl coated aluminum in an overlabelled

carton containing 28 tablets.

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

No special instructions.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1659/27/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010

10 DATE OF REVISION OF THE TEXT

April 2012