Annex II

Amendments to the Summary of Product Characteristics and Package Leaflet

This Summary of Product Characteristics and package leaflet is the outcome of the referral procedure and valid at the time of the Commission Decision.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR CRESTOR AND ASSOCIATED NAMES

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[The wording of the indication for treatment of hypercholesterolaemia should be replaced with the following:]

Treatment of hypercholesterolaemia
Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

4.2 Posology and method of administration

[Existing information on the paediatric population should be replaced with the following:]

Paediatric population
Paediatric use should only be carried out by specialists.

Children and adolescents 6 to 17 years of age (Tanner Stage <II-V)
In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily.

- In children 6 to 9 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-10 mg orally once daily. Safety and efficacy of doses greater than 10 mg have not been studied in this population.
- In children 10 to 17 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-20 mg orally once daily. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations (see Section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment.

Experience in children with homozygous familial hypercholesterolaemia is limited to a small number of children aged between 8 and 17 years.

The 40 mg tablet is not suitable for use in paediatric patients.

Children younger than 6 years
The safety and efficacy of use in children younger than 6 years has not been studied. Therefore, Crestor is not recommended for use in children younger than 6 years.

4.4 Special warnings and precautions for use

[Existing information on the paediatric population should be replaced with the following:]

Paediatric population
The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 6 to 17 years of age taking rosuvastatin

is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see Section 5.1).

In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults (see Section 4.8).

5.1 Pharmacodynamic properties

[Existing information on the paediatric population should be replaced with the following:]

Paediatric population
In a double-blind, randomized, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, rosuvastatin dose-titration phase, patients 10-17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10-13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/l.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see Section 4.4). This trial (n=176) was not suited for comparison of rare adverse drug events.

Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolaemia aged 6 to 17 years (88 male and 110 female, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.

After 24 months of treatment with rosuvastatin, the LS mean percent reduction from the baseline value in LDL-C was -43% (Baseline: 236 mg/dL, Month 24: 133 mg/dL). For each age group, the LS mean percent reductions from baseline values in LDL-C were -43% (Baseline: 234 mg/dL, Month 24: 124 mg/dL), -45% (Baseline: 234 mg/dL, 124 mg/dL), and -35% (Baseline: 241 mg/dL, Month 24: 153 mg/dL) in the 6 to <10, 10 to <14, and 14 to <18 age groups, respectively.

Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C,LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non HDL C/HDL-C, ApoB, ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.

No effect on growth, weight, BMI or sexual maturation was detected after 24 months of treatment (see Section 4.4).

The European Medicines Agency has waived the obligation to submit the results of studies with rosuvastatin in all subsets of the paediatric population in the treatment of homozygous familial hypercholesterolaemia, primary combined (mixed) dyslipidaemia and in the prevention of cardiovascular events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

[Existing information on the paediatric population should be replaced with the following:]

Paediatric population: Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10-17 or 6-17 years of age (total of 214

patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE PACKAGE LEAFLET FOR CRESTOR AND ASSOCIATED NAMES

1. What CRESTOR is and what it is used for

[Existing wording of this section should be replaced with the following:]

CRESTOR belongs to a group of medicines called statins.

You have been prescribed CRESTOR because:

- You have a high cholesterol level. This means you are at risk from a heart attack or stroke. Crestor is used in adults, adolescents and children 6 years or older to treat high cholesterol.

You have been advised to take a statin, because changing your diet and taking more exercise were not enough to correct your cholesterol levels. You should continue with your cholesterol-lowering diet and exercise while you are taking CRESTOR.

Or

- You have other factors that increase your risk of having a heart attack, stroke or related health problems.

2. What you need to know before you take CRESTOR

[Existing information on the paediatric population should be replaced with the following:]

Children and adolescents

• **If the patient is under 6 years old:** CRESTOR should not be given to children younger than 6 years.

• **If the patient is below 18 years of age:** The CRESTOR 40 mg tablet is not suitable for use in children and adolescents below 18 years of age.

3. How to take CRESTOR

[Existing information on the paediatric population should be replaced with the following:]

Use in children and adolescents aged 6–17 years

The usual start dose is 5 mg. Your doctor may increase your dose to find the right amount of CRESTOR for you. The maximum daily dose of CRESTOR is 10 mg for children aged 6 to 9 years and 20 mg for children aged 10 to 17 years. Take your dose once a day. CRESTOR 40 mg tablet should not be used by children.