Public Assessment Report
CREZET 10/5

INFORMASI PRODUK

Nama obat	:	**CREZET 10/5**
Bentuk sediaan	:	TABLET SALUT SELAPUT
Zat aktif	:	Tiap tablet salut selaput mengandung: - Rosuvastatin calcium 5,20 mg ~ Rosuvastatin 5,00 mg - Ezetimibe 10 mg
Kemasan	:	Dus, 3 blister @ 10 tablet salut selaput
Pendaftar	:	PT. Daewoong Infion, Indonesia
Produsen	:	Daewoong Pharmaceutical Co., Ltd.., Cheongju-Si, Republic Of Korea
Kategori Registrasi	:	Registrasi obat dengan kekuatan baru
Indikasi yang diajukan:	:	*Primary hypercholesterolemia* *CREZET is administered as an adjunct to a diet to reduce elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apo-B protein (Apo B), triglycerides (TG), and non-HDL-cholesterol, and to increase HDL-cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia.* *Many risk factors should be considered when administering lipid modifiers to patients with an increased risk of atherosclerotic vascular disease due to hypercholesterolemia. Lipid modifiers should be used in conjunction with an appropriate diet (including saturated fat and cholesterol restriction) and should be used in cases of insufficient response to diet and other non-pharmacological measures.* *Prior to administration of CREZET, other secondary causes of dyslipidemia (e.g., diabetes, hypothyroidism, obstructive hepatic disease, chronic renal failure, drugs that increase LDL-cholesterol and drugs that decrease HDL-cholesterol [progestin, anabolic steroid, and corticosteroid]), and if necessary, secondary causes should be treated. The lipid test should include total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. If triglyceride levels are 400 mg/dL or more (>4.5 mmol/L), the LDL-cholesterol concentration should be determined by ultracentrifugation. In the case of hospitalization due to an acute coronary accident, lipids should be measured at the time of admission or within 24 hours after admission. This measurement can be used as a reference for initiating LDL-lowering therapy before or at the time of patient's discharge.*
Posologi yang diajukan	:	*CREZET is administered once a day regardless of meals.* *Prior to or under CREZET, patients must continue on a standard cholesterol-lowering diet. The dosage of CREZET should be adjusted according to the patient's baseline LDL-cholesterol level, the recommended therapeutic target, and the patient's response.* *Posology* *Primary hypercholesterolemia* *The dosage range of CREZET is 10/5 mg to 10/20 mg per day. A starting dose of 10/5 mg per day is recommended. For patients who require more LDL-cholesterol reduction, the dosage may be adjusted. After starting CREZET or after titrating the dose, check the blood lipid level at an interval of at least 4 weeks and adjust the dose accordingly. The dose can be increased to a maximum of 10/20 mg per day.*

Patients who are taking ezetimibe and rosuvastatin in combination may switch to CREZET (fix-dose combination with the same content of each API) for their convenience.
Paediatric population: The safety and efficacy of Rosuvastatin/Ezetimibe in children below the age of 18 years has not yet been established." Rosuvastatin/Ezetimibe is not suitable for initial therapy.

PENGANTAR

CREZET 10/5 merupakan obat dengan zat aktif Rosuvastatin calcium dan Ezetimibe. Rosuvastatin adalah Inhibitor HMG-CoA Reduktase, yang menghambat sintesis kolesterol di hati dengan menghambat secara kompetitif HMG-CoA reduktase, yaitu enzim yang bekerja pada langkah pembatas laju biosintesis kolesterol, di mana HMG-CoA diubah menjadi asam mevalonat. Ezetimibe merupakan inhibitor penyerapan kolesterol selektif yang menghambat penyerapan kolesterol dari makanan dan empedu ke dalam sirkulasi enterohepatik dengan cara bekerja pada protein NPC1L1, yaitu reseptor penyerapan kolesterol di vili usus halus, tanpa mempengaruhi penyerapan asam empedu, asam lipid, trigliserida dan vitamin yang larut dalam lemak.
Mengingat registrasi obat CREZET 10/5 adalah dengan kekuatan baru, saat ini evaluasi difokuskan pada evaluasi data uji klinik, dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut.

ASPEK MUTU

CREZET 10/5 mengandung zat aktif Rosuvastatin calcium 5,20 mg ~ Rosuvastatin 5,00 mg dan Ezetimibe 10 mg. Obat mengandung eksipien low-substituted hydroxypropyl cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, lactose monohydrate, hydroxypropylcellulose, magnesium stearate, alcohol, air, dan kombinasi-opadry pink 03B54445.

Zat Aktif

Zat aktif rosuvastatin merupakan bubuk amorf berwarna putih hingga putih pudar, sedangkan ezetimibe merupakan bubuk kristal berwarna putih hingga putih pucat.
Kedua zat aktif yang digunakan dalam produk Crezet telah digunakan dalam sediaan lain yang telah disetujui beredar di Indonesia. Evaluasi mutu kedua zat aktif tersebut mengacu pada produk yang telah disetujui.

Obat jadi

Obat jadi diproduksi dalam bentuk tablet salut selaput yang dibuat secara granulasi basah. Proses pembuatannya obat dilakukan mulai dari penimbangan bahan baku, pencampuran, granulasi, pengeringan, pencetakan tablet, pembuatan larutan penyalut, penyalutan, dan pengemasan. Telah dilakukan identifikasi terhadap tahapan kritikal, termasuk *in-process controls* yang dilakukan pada masing-masing tahapan tersebut. Validasi proses telah dilakukan terhadap 3 bets skala komersil. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.
Spesifikasi obat telah ditetapkan yaitu pemerian (visual), identifikasi (HPLC), disolusi (HPLC), keseragaman kandungan (HPLC), pengotor (HPLC), assay (HPLC), pelarut sisa, kadar air, dan batas mikroba. Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat kritikal zat aktif dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.
Data stabilitas dari 3 bets kala komersil dengan hasil memenuhi spesifikasi dan tidak ada perubahan signifikan. Penyimpanan produk yang dapat disetujui adalah Store below 30 ℃ selama 36 bulan.
Kesimpulan
Dari aspek mutu, CREZET 10/5 tablet salut selaput dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Klinik

1. Berdasarkan hasil studi DP-CTR207-III-02 yang membandingkan kombinasi Ezetimibe / Rosuvastatin 10/5 mg, 10/10 mg, dan 10/20 mg terhadap masing-masing sediaan tunggal Rosuvastatin 5 mg, 10 mg, dan 20 mg pada pasien dengan hiperkolesterolemia primer selama 8 minggu menunjukkan:
   a. Penurunan kadar *Cholesterol Low Density Lipoprotein* (LDL-C) lebih tinggi pada kelompok kombinasi Ezetimibe / Rosuvastatin dibandingkan monoterapi Rosuvastatin.
      - LS *mean percent change* Ezetimibe / Rosuvastatin 5/10 mg dibandingkan dengan Rosuvastatin 5 mg: -58,56±2,02% vs. -43,61±1,90%, 95% CI: 10,41, 19,48, p<0,0001).
      - LS *mean percent change* Ezetimibe / Rosuvastatin 10/10 mg dibandingkan dengan Rosuvastatin 10 mg: -61,11±2,37 vs. -52,83±2,46%, 95% CI: 2,72, 13.85, p=0,0039).
      - *LS mean percent change* Ezetimibe / Rosuvastatin 20/10 mg dibandingkan dengan Rosuvastatin 20 mg: -65 .63±2.95% vs. -55.76±3.07%, 95% CI: 3.35, 16.40, p=0,0033).
   b. Penurunan kadar *total cholesterol* (TC) juga didapatkan lebih tinggi pada kelompok kombinasi Ezetimibe / Rosuvastatin dibandingkan monoterapi Rosuvastatin.
      - LS *mean percent change* Ezetimibe / Rosuvastatin 5/10 mg dibandingkan dengan Rosuvastatin 5 mg: -42.20 ±1.55 vs.-29.41 ±1.46, p<0,0001),
      - LS *mean percent change* Ezetimibe / Rosuvastatin 10/10 mg dibandingkan dengan Rosuvastatin 10 mg: -42.95 ±1.74 vs.-37.13 ±1.78, p=0,0050),
      - LS *mean percent change* Ezetimibe / Rosuvastatin 20/10 mg dibandingkan dengan Rosuvastatin 20 mg: -45.19 ±2.23 vs. -38.01 ±2.31, p=0,0045).
   c. Profil keamanan kombinasi Ezetimibe / Rosuvastatin sebanding dengan monoterapi Rosuvastatin (42 (22,11%) vs 38 (20,32%), p=0,6718), dan tidak ada *Serious Adverse Events* yang ditemukan.
2. Berdasarkan studi bioekivalensi DDS19-004BE yang membandingkan profil farmakokinetik tablet Ezetimibe / Rosuvastatin 10/20 mg produksi Daewoong Pharmaceutical Co. Ltd, Korea dengan tablet Ezetimibe / Rosuvastatin 10/20 mg produksi Alvogen Korea Co. Ltd., Korea pada subjek sehat menunjukkan hasil yang biokivalen berdasarkan parameter sebagai berikut:
   a. Ezetimibe:
      - AUC: GMR 1,0200 (90% CI: 0,9568-1,0873), CV intra-subject: 20,41%
      - Cmax: GMR 1,0858 (90% CI: 0,9710-1.2141), CV intra-subject: 36,46%
   b. Rosuvastatin
      - AUC: GMR 1,0004 (90% CI: 0.9544-1,0487), CV intra-subject: 14,98%
      - Cmax: GMR 0,9882 (90% CI: 0,9256-1,0551), CV intra-subject: 20,91
3. Berdasarkan hasil uji disolusi terbanding, Crezet tablet 10/20 mg (nomor bets A91389) ekivalen dengan Crezet tablet 10/5 mg (nomor bets G00015) produksi Daewoong Pharmaceutical berdasarkan parameter:
   a. Laju disolusi rosuvastatin pada obat uji dan obat pembanding untuk kondisi pH 1,2; buffer pH 4,0; buffer pH 6,8; dan air adalah di atas 85% setelah 15 menit.
   b. Laju disolusi ezetimibe pada obat uji dan obat pembanding untuk kondisi pH 7 + 0,5% SDS adalah di atas 85% setelah 15 menit.

KEPUTUSAN

Berdasarkan hal tersebut di atas, registrasi kekuatan baru CREZET 10/5 Tablet Salut Selaput diterima dengan indikasi sebagai berikut :

Primary hypercholesterolemia

CREZET is administered as an adjunct to a diet to reduce elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apo-B protein (Apo B), triglycerides (TG), and non-HDL-cholesterol, and to increase HDL-cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia.

Many risk factors should be considered when administering lipid modifiers to patients with an increased risk of atherosclerotic vascular disease due to hypercholesterolemia. Lipid modifiers should be used in conjunction with an appropriate diet (including saturated fat and cholesterol restriction) and should be used in cases of insufficient response to diet and other non-pharmacological measures.

Prior to administration of CREZET, other secondary causes of dyslipidemia (e.g., diabetes, hypothyroidism, obstructive hepatic disease, chronic renal failure, drugs that increase LDL-cholesterol and drugs that decrease HDL-cholesterol [progestin, anabolic steroid, and corticosteroid]), and if necessary, secondary causes should be treated. The lipid test should include total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. If triglyceride levels are 400 mg/dL or more (>4.5 mmol/L), the LDL-cholesterol concentration should be determined by ultracentrifugation. In the case of hospitalization due to an acute coronary accident, lipids should be measured at the time of admission or within 24 hours after admission. This measurement can be used as a reference for initiating LDL-lowering therapy before or at the time of patient's discharge.

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PRODUCT INFORMATION

Drug name	:	**CREZET 10/5**
Dosage form	:	FILM-COATED TABLETS
Active substances	:	Each film-coated tablet contains: - Rosuvastatin calcium 5.20 mg ~ Rosuvastatin 5.00 mg - Ezetimibe 10 mg
Packaging	:	Box of 3 blisters @ 10 film-coated tablets
Applicant	:	PT. Daewoong Infion, Indonesia
Manufacturer	:	Daewoong Pharmaceutical Co., Ltd.., Cheongju-Si, Republic Of Korea
Registration Categories	:	Registration of drug with new strength
Proposed Indication:	:	*Primary hypercholesterolemia* *CREZET is administered as an adjunct to a diet to reduce elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apo-B protein (Apo B), triglycerides (TG), and non-HDL-cholesterol, and to increase HDL-cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia.* *Many risk factors should be considered when administering lipid modifiers to patients with an increased risk of atherosclerotic vascular disease due to hypercholesterolemia. Lipid modifiers should be used in conjunction with an appropriate diet (including saturated fat and cholesterol restriction) and should be used in cases of insufficient response to diet and other non-pharmacological measures.* *Prior to administration of CREZET, other secondary causes of dyslipidemia (e.g., diabetes, hypothyroidism, obstructive hepatic disease, chronic renal failure, drugs that increase LDL-cholesterol and drugs that decrease HDL-cholesterol [progestin, anabolic steroid, and corticosteroid]), and if necessary, secondary causes should be treated.* *The lipid test should include total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. If triglyceride levels are 400 mg/dL or more (>4.5 mmol/L), the LDL-cholesterol concentration should be determined by ultracentrifugation. In the case of hospitalization due to an acute coronary accident, lipids should be measured at the time of admission or within 24 hours after admission. This measurement can be used as a reference for initiating LDL-lowering therapy before or at the time of patient's discharge.*
Proposed dosage and administration	:	*CREZET is administered once a day regardless of meals.* *Prior to or under CREZET, patients must continue on a standard cholesterol-lowering diet. The dosage of CREZET should be adjusted according to the patient's baseline LDL-cholesterol level, the recommended therapeutic target, and the patient's response.* *Dosage* *Primary hypercholesterolemia* *The dosage range of CREZET is 10/5 mg to 10/20 mg per day. A starting dose of 10/5 mg per day is recommended. For patients who require more LDL-cholesterol reduction, the dosage may be adjusted. After starting CREZET or after titrating the dose, check the blood lipid level at an interval of at least 4 weeks and adjust the dose accordingly. The dose can be increased to a maximum of 10/20 mg per day.*

Patients who are taking ezetimibe and rosuvastatin in combination may switch to CREZET (fix-dose combination with the same content of each API) for their convenience.
Paediatric population: The safety and efficacy of Rosuvastatin/Ezetimibe in children below the age of 18 years has not yet been established." Rosuvastatin/Ezetimibe is not suitable for initial therapy.

INTRODUCTION

CREZET 10/5 is a drug with the active substances Rosuvastatin calcium and Ezetimibe. Rosuvastatin is a HMG-CoA Reductase Inhibitor, which inhibits cholesterol synthesis in the liver by competitively inhibiting HMG-CoA reductase, an enzyme that acts in the rate-limiting step of cholesterol biosynthesis where HMG-CoA is converted to mevalonic acid. Ezetimibe is a selective cholesterol absorption inhibitor which suppresses absorption of cholesterol from dietary intake and from bile in the enterohepatic circulation by acting on NPC1L1 protein, a cholesterol absorption receptor in the villi of small intestine, without effect on absorption of bile acid, lipid acid, triglyceride and fat-soluble vitamins. Considering that the registration of CREZET 10/5 drugs is with new strength, the current evaluation is focused on evaluating clinical trial data and drug quality to further prove efficacy, safety, and drug quality.

QUALITY ASPECT

CREZET 10/5 contains the active substances Rosuvastatin calcium 5.20 mg ~ Rosuvastatin 5.00 mg and Ezetimibe 10 mg. The drug contains excipients low-substituted hydroxypropyl cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, lactose monohydrate, low substituted hydroxypropylcellulose, magnesium stearate, alcohol, water, and combination-opadry pink 03B54445.

Active Substances

The active substance rosuvastatin is a white to off-white powder, while ezetimibe is a white to an off-white crystalline powder. Both active ingredients used in Crezet products have been used in other preparations that have been approved for circulation in Indonesia. The quality evaluation of the two active substances refers to the approved product.

Finished Drug Product

The finished drug is formulated in the form of film-coated tablets made by wet granulation. The manufacturing process of drugs is carried out starting from weighing raw materials, mixing, granulation, drying, printing tablets, making coating solutions, packaging, and packaging. Identification of critical stages has been carried out, including in-process controls carried out at each of these stages. Process validation has been carried out on 3 commercial-scale batches. The results of the process validation show the ability of the process to produce finished drugs that meet the set acceptance criteria.
Drug specifications have been determined, which are description (visual), identification (HPLC), dissolution (HPLC), uniformity of content (HPLC), impurities (HPLC), assay (HPLC), residual solvents, moisture content, and microbial limits. The parameters in the specification are selected based on the physicochemical characteristics and critical properties of the active substance by considering, among others, the results of the batch test used in clinical trials and long-term stability data. The analytical method used has been validated. The results of the batch analysis provide results that meet the required specifications.
Stability data from 3 commercial batches with results meeting specifications and no significant changes. The storage of approved products is Store below 30 °C for 36 months.
Conclusion
From the quality aspect, CREZET 10/5 film-coated tablets is considered acceptable.

EFFICACY AND SAFETY ASPECTS

Clinical Studies

1. Based on the results of the DP-CTR207-III-02 study comparing Ezetimibe/Rosuvastatin combinations of 10/5 mg, 10/10 mg, and 10/20 mg against a single Rosuvastatin preparation of 5 mg, 10 mg, and 20 mg respectively in patients with primary hypercholesterolemia for 8 weeks showed:
   a. The decrease in *Low Density Lipoprotein* (LDL-C) cholesterol levels was higher in the Ezetimibe/Rosuvastatin combination group compared to Rosuvastatin monotherapy.
      - LS *mean percent change* of Ezetimibe/Rosuvastatin 5/10 mg compared to Rosuvastatin 5 mg: -58.56±2.02% vs. -43.61±1.90%, 95% CI: 10.41, 19.48, p<0.0001).
      - LS *mean percent change* of Ezetimibe/Rosuvastatin 10/10 mg compared to Rosuvastatin 10 mg: -61.11±2.37 vs. -52.83±2.46%, 95% CI: 2.72, 13.85, p=0.0039).
      - *LS mean percent change* Ezetimibe/Rosuvastatin 20/10 mg compared to Rosuvastatin 20 mg: -65 .63±2.95% vs. -55.76±3.07%, 95% CI: 3.35, 16.40, p=0.0033).
   b. The reduction in *total cholesterol* (TC) levels was also higher in the Ezetimibe/Rosuvastatin combination group compared to Rosuvastatin monotherapy.
      - LS *mean percent change* Ezetimibe/Rosuvastatin 5/10 mg compared to Rosuvastatin 5 mg: -42.20 ±1.55 vs.-29.41 ±1.46, p<0.0001),
      - LS *mean percent change* Ezetimibe/Rosuvastatin 10/10 mg compared to Rosuvastatin 10 mg: -42.95 ±1.74 vs.-37.13 ±1.78, p=0.0050),
      - LS *mean percent change* Ezetimibe/Rosuvastatin 20/10 mg compared to Rosuvastatin 20 mg: -45.19 ±2.23 vs. -38.01 ±2.31, p=0.0045).
   c. The safety profile of the combination of Ezetimibe/Rosuvastatin was comparable to Rosuvastatin monotherapy (42 (22.11%) vs 38 (20.32%), p=0.6718), and no *Serious Adverse Events* were found.
2. Based on the DDS19-004BE bioequivalence study comparing the pharmacokinetic profile of Ezetimibe/Rosuvastatin 10/20 mg tablets produced by Daewoong Pharmaceutical Co. Ltd, Korea with Ezetimibe/Rosuvastatin 10/20 mg tablets produced by Alvogen Korea Co. Ltd., Korea in healthy subjects showed biokinetic results based on the following parameters:
   a. Ezetimibe:
      - AUC: GMR 1.0200 (90% CI: 0.9568-1.0873), intra-subject CV: 20.41%
      - Cmax: GMR 1.0858 (90% CI: 0.9710-1.2141), intra-subject CV: 36.46%
   b. Rosuvastatin
      - AUC: GMR 1.0004 (90% CI: 0.9544-1.0487), intra-subject CV: 14.98%
      - Cmax: GMR 0.9882 (90% CI: 0.9256-1.0551), intra-subject CV: 20.91
3. Based on the results of the comparative solution test, Crezet tablets 10/20 mg (batch number A91389) are equivalent to Crezet tablets 10/5 mg (batch number G00015) produced by Daewoong Pharmaceutical based on the following parameters:
   a. The dissolution rate of rosuvastatin in test drugs and comparator drugs for pH conditions of 1.2; buffer pH 4.0; pH buffer 6.8; and the water is above 85% after 15 minutes.
   b. The solution rate of ezetimibe in test drugs and comparator drugs for pH 7 + 0.5% SDS conditions is above 85% after 15 minutes.

DECISION

Based on the above, the registration of new strength of CREZET 10/5 Film-Coated Tablets is approved with the following indications:

Primary hypercholesterolemia

CREZET is administered as an adjunct to a diet to reduce elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apo-B protein (Apo B), triglycerides (TG), and non-HDL-cholesterol, and to increase HDL-cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia.

Many risk factors should be considered when administering lipid modifiers to patients with an increased risk of atherosclerotic vascular disease due to hypercholesterolemia. Lipid modifiers should be used in conjunction with an appropriate diet (including saturated fat and cholesterol restriction) and should be used in cases of insufficient response to diet and other non-pharmacological measures.

Prior to administration of CREZET, other secondary causes of dyslipidemia (e.g., diabetes, hypothyroidism, obstructive hepatic disease, chronic renal failure, drugs that increase LDL-cholesterol and drugs that decrease HDL-cholesterol [progestin, anabolic steroid, and corticosteroid]), and if necessary, secondary causes should be treated. The lipid test should include total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. If triglyceride levels are 400 mg/dL or more (>4.5 mmol/L), the LDL-cholesterol concentration should be determined by ultracentrifugation. In the case of hospitalization due to an acute coronary accident, lipids should be measured at the time of admission or within 24 hours after admission. This measurement can be used as a reference for initiating LDL-lowering therapy before or at the time of patient's discharge.