# Clinical Pharmacology Review

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| **NDA** | 21-445 SE5 020 |
| **Submission Dates** | December 14, 2007 |
| **Brand Name** | ZETIA ™ |
| **Generic Name** | Ezetimibe |
| **Reviewer** | S.W. Johnny Lau, R.Ph., Ph.D. |
| **Team Leader** | Sally Y. Choe, Ph.D. |
| **OCP Division** | Clinical Pharmacology 2 (HFD-870) |
| **OND Division** | Metabolism and Endocrinology Products (HFD-510) |
| **Sponsor** | Schering-Plough |
| **Formulation; Strength** | Oral immediate release tablet; 10 mg tablet |
| **Relevant IND** | 52,791 |
| **Submission Type; Code** | Supplement; S |
| **Indication** | Treatment of primary hypercholesterolemia |

## Background

NDA 21-445 SE5 020 does not contain new Clinical Pharmacology information. However, the sponsor submitted proposed labeling changes in PLR format for review.

## Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) reviewed 21-445 SE5 020's proposed Clinical Pharmacology labeling changes. The major recommended change was to replace the text with the tables below for the "Drug Interactions" section in 12.3 Pharmacokinetics. Please see other recommendations in the approved labeling.

### 12.3 Pharmacokinetics

*Drug Interactions [See also Drug Interactions (7)]*

**Table 5**
**Effect of Co-administered Drugs on Total Ezetimibe**

| Co-administered drug and dosing regimen | Total ezetimibe * | |
|---|---|---|
| | Change in AUC | Change in $C_{max}$ |
| Cyclosporine- stable dose required (75-150 mg BID)†,** | ↑240% | ↑290% |
| Fenofibrate, 200 mg QD, 14 days† | ↑48% | ↑64% |
| Gemfibrozil, 600 mg BID, 7 days† | ↑64% | ↑91% |
| Cholestyramine, 4 g BID, 14 days† | ↓55% | ↓4% |
| Aluminum & magnesium hydroxide combination antacid, single dose§ | ↓4% | ↓30% |
| Cimetidine 400 mg BID, 7 days | ↑6% | ↑22% |
| Glipizide 10 mg, single dose | ↑4% | ↓8% |
| **Statins** | | |
| Lovastatin 20 mg QD, 7 days | ↑9% | ↑3% |
| Pravastatin 20 mg QD, 14 days | ↑7% | ↑23% |
| Atorvastatin 10 mg QD, 14 days | ↓2% | ↑12% |
| Rosuvastatin 10 mg QD, 14 days | ↑13% | ↑18% |
| Fluvastatin 20 mg QD, 14 days | ↓19% | ↑7% |

* Based on 10 mg dose of ezetimibe

** Post-renal transplant patients with mild impaired or normal renal function. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73m$^2$) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects.

† See 7 Drug Interactions

§ Supralox®, 20 mL

**Table 6**
**Effect of Ezetimibe Co-Administration on Systemic Exposure to Other Drugs**

| Co-administered Drug and its Dosage Regimen | Ezetimibe Dosage Regimen | Change in AUC of Co-administered Drug | Change in $C_{max}$ of Co-administered Drug |
|---|---|---|---|
| Warfarin, 25 mg single dose on day 7 | 10 mg QD, 11 days | ↓2%(R-warfarin)<br>↓4% (S-warfarin) | ↑3% (R-warfarin)<br>↑1% (S-warfarin) |
| Digoxin, 0.5 mg single dose | 10 mg QD, 8 days | ↑2% | ↓7% |
| Gemfibrozil, 600mg BID, 7 days† | 10 mg QD, 7 days | ↓1% | ↓11% |
| Ethinyl estradiol & Levonorgestrel QD, 21 days | 10 mg QD, days 8-14 of 21d oral contraceptive cycle | Ethinyl estradiol<br>0%<br>Levonorgestrel<br>0% | Ethinyl estradiol<br>↓9%<br>Levonorgestrel<br>↓5% |
| Glipizide, 10 mg on days 1 and 9 | 10 mg QD, days 2-9 | ↓3% | ↓5% |
| Fenofibrate 200 mg QD, 14 days† | 10 mg QD, 14 days | ↑11% | ↑7% |
| Cyclosporine 100 mg single dose day 7† | 20 mg QD, 8 days | ↑15% | ↑10% |
| **Statins** | | | |
| Lovastatin 20 mg QD, 7 days | 10 mg QD, 7 days | ↑19% | ↑3% |
| Pravastatin 20 mg QD, 14 days | 10 mg QD, 14 days | ↓20% | ↓24% |
| Atorvastatin 10 mg QD, 14 days | 10 mg QD, 14 days | ↓4% | ↑7% |
| Rosuvastatin 10 mg QD, 14 days | 10 mg QD, 14 days | ↑19% | ↑17% |
| Fluvastatin 20 mg QD, 14 days | 10 mg QD, 14 days | ↓39% | ↓27% |

† See 7 Drug Interactions

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FT signed by Sally Choe, Ph.D., Team Leader 6/ /08

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/s/
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