怡妥® 錠 10 公絲

EZETROL® 10 mg Tablets

(Ezetimibe)

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衛署藥輸字第 024058 號
本藥須由醫師處方使用

藥物主成分

EZETROL 為口服錠劑，每錠含有 10 mg ezetimibe。

臨床治療類別

EZETROL®(ezetimibe)是新一類的降血脂藥品，它可以選擇性抑制膽固醇以及相關植物固醇在腸胃道的吸收。

作用機轉

EZETROL 於口服之後，具活性且有效，具有不同於其他類型降膽固醇化合物(如：statins，降膽酸藥物(bile acid sequestrants) [resins]，fibric acid 衍生物，plant stanols)的獨特作用機轉。Ezetimibe 作用的分子目標為固醇載體(sterol transporter) Niemann-Pick C1-Like 1 (NPC1L1)，該載體負責膽固醇及植物固醇在小腸的吸收。

Ezetimibe主要作用於小腸的刷狀邊緣而抑制膽固醇的吸收，進而降低腸內膽固醇輸送至肝臟。如此可以減少肝臟中膽固醇的儲存，並增加血液中膽固醇的清除。Ezetimibe不會增加膽酸的分泌(像bile acid sequestrants)，也不會抑制肝臟合成膽固醇(像statins)。曾進行一系列的臨床前試驗來決定ezetimibe在抑制膽固醇吸收方面的選擇性。Ezetimibe可以抑制^{14}C-cholesterol的吸收，但是對三酸甘油酯、脂肪酸、膽酸、progesterone、ethinyl estradiol或是脂溶性維生素A及D的吸收都沒有影響。在大鼠、狗、兔子所進行的毒性試驗中，可見到ezetimibe與HMG-CoA reductase抑制劑間有藥物動力學上的交互作用。在人類，當ezetimibe與HMG-CoA reductase抑制劑併用時，並沒有看到具臨床意義的藥物動力學交互作用發生(請參見藥物交互作用)。

針對 18 位高膽固醇血症的病人進行為期兩週的臨床試驗發現，EZETROL 與安慰劑相較時，可以抑制腸內膽固醇的吸收達 54%。藉由抑制腸內膽固醇的吸收，ezetimibe 會使輸送至肝臟的膽固醇減少。Statins 的主要作用為減少肝臟合成膽固醇。若將這兩種不同作用機轉的藥品合併使用，將可以產生互補作用而達到降低膽固醇的效果。EZETROL 和 statin 類藥品合併投與用於治療高膽固醇血症病人時，可以降低總血漿膽固醇(total plasma cholesterol; total-C)、低密度脂蛋白膽固醇(low-density lipoprotein cholesterol; LDL-C)、apolipoprotein B (Apo B)，以及三酸甘油酯(triglycerides; TG)，也可增加高密度脂蛋白膽固醇(High-density lipoprotein cholesterol; HDL-C)；兩種藥品一起使用比單獨使用的效果為佳。混合性高血脂的病患併服 EZETROL 和 fenofibrate 可有效改善血漿中 total-C、LDL-C、Apo B、TG、HDL-C 以及 non-HDL-C。

臨床研究指出，total-C、LDL-C 和 Apo B(Apo B 為 LDL 的主要組成蛋白)的濃度升高，會促成人體粥狀動脈硬化的發生。此外，HDL-C 的濃度降低同樣也與粥狀動脈硬化的發生有關。流行病學的研究已經證實，心血管疾病的罹病率及致死率與 total-C 和 LDL-C 的濃度成正比，而和 HDL-C 的濃度成反比。此外，富含膽固醇和三酸甘油酯的脂蛋白，其中包括極低密度脂蛋白(very-low-density lipoprotein cholesterol; VLDL)，中密度脂蛋白(intermediate-density lipoprotein; IDL)及其殘留物，同樣地會促成粥狀動脈硬化的發生。

藥物動力學

吸收

Ezetimibe 在口服之後會很快被吸收，大部分被代謝成具有藥理活性的 phenolic glucuronide(ezetimibe－ glucuronide)。Ezetimibe－ glucuronide 及 ezetimibe 達到平均最高血漿濃度(Cmax)的時間分別為 1-2 小時及 4-12 小時。因為此化合物不溶於水性溶劑中而不適宜注射，因此，無法測定 ezetimibe 的絕對生體可用率。EZETROL 10 mg 錠劑與食物一起服用，無論是高脂肪或無脂肪含量的飲食都不會影響 ezetimibe 的口服生體可用率。因此，餐間或空腹時均可服用 EZETROL。

分佈

Ezetimibe 和 ezetimibe－ glucuronide 與人類血漿蛋白質的結合率分別為 99.7%和 88~92%。

代謝

Ezetimibe 主要在小腸及肝臟經由 glucuronide conjugation 被代謝(第二相反應)，再經由膽汁排除。在所有不同種的試驗動物身上曾觀察到極小量氧化性代謝(第一相反應)。血漿中主要偵測到的藥品衍生物是 ezetimibe 和 ezetimibe－glucuronide，分別約占血漿中藥品總量的 10-20%和 80-90%。Ezetimibe 和 ezetimibe－ glucuronide 會經由腸肝循環，因此自血漿排除的速度緩慢。Ezetimibe 和 ezetimibe－ glucuronide 的半衰期約 22 小時。

排泄

人體口服^{14}C- ezetimibe(20 mg)之後，在血漿中所測得的ezetimibe總量約佔所有放射線活性計數的 93%。經過十天的收集，所給予的放射線活性約有 78%和 11%分別在糞便及尿液中回收。48 小時後，血漿中已無可偵測到的放射線活性。

病人特性「特殊族群」

兒童

兒童、青少年(10 至 18 歲)及成人間對於 ezetimibe 的吸收和代謝情形類似。由 ezetimibe 總濃度來看，青少年以及成人之間並無藥動學上的差異。目前並無小於十歲之兒童族群的藥動學資料。

老人

血漿中的 ezetimibe 總濃度，老年人(≧ 65 歲)約為年輕人(18 到 45 歲)的 2 倍，而服用 ezetimibe 的老年人和年輕人在 LDL-C 的降低和安全性方面則是類似。所以，老年人不需要調整劑量。

肝功能不全

輕度肝功能不全的病人(Child Pugh score 5 to 6)在服用單一劑量 10 mg 的 ezetimibe 之後，總 ezetimibe 的血中濃度曲線下面積(AUC)平均值約為正常人的 1.7 倍。在一個每天給予 ezetimibe 10 mg，為期 14 天的多次劑量的研究中，有中度肝功能不全病人(Child Pugh score 7 to 9)的總 ezetimibe 的 AUC 平均值，在第一天及第十四天均比正常人約高 4 倍。輕度肝功能不全的病人不需要調整劑量。因為 ezetimibe 使用於中度或重度肝功能不全(Child Pugh score > 9)之病人的影響不明，所以這群病人不建議服用 ezetimibe(請參見注意事項)。

腎功能不全

嚴重腎臟疾病的病人(n=8，平均CrCl≦ 30 ml/min/1.73 m^2)在服用單一劑量 10 mg 的ezetimibe之後，總ezetimibe的AUC平均值比正常人(n=9)約高 1.5 倍。這樣的結果並不具臨床意義，故腎功能受損的病人不需要調整劑量。

本試驗中另外的病患(腎臟移植後及給予多重藥物，包括 cyclosporine)總 ezetimibe 的暴露量高達 12 倍。

性別

血漿中的總 ezetimibe 濃度，女性比男性略高(＜20%)，而服用 ezetimibe 的女性和男性在 LDL-C 的降低和安全性方面則是類似。所以，並不需要根據性別來調整劑量。

種族

根據一項藥動學研究的 meta-analysis，黑人與白種人之間並無藥動學上的差異。

臨床試驗

原發性高膽固醇血症

單方治療

在兩項為期十二週、針對 1719 位患有原發性高膽固醇血症的病人執行的多中心、雙盲性，以安慰劑對照之研究中，EZETROL 10 mg 顯著地比安慰劑更有效地降低 total-C、LDL-C、Apo B 及 TG，並且增加 HDL-C(參見表一)。其降低 LDL-C 的功效不因年齡、性別、種族及接受試驗治療前的 LDL-C 值的差異而有所不同。此外，EZETROL 對血中脂溶性維生素 A、D 及 E 的濃度、凝血時間及腎上腺皮質激素的分泌都沒有影響。

表一：原發性高膽固醇血症病人服用 EZETROL 之後的平均反應
(與試驗前基礎值的差異平均值百分比)

	治療組別	人數	Total-C	LDL-C	Apo B	TG[a]	HDL-C
試驗一	安慰劑	205	+1	+1	-1	-1	-1
	EZETROL	622	-12	-18	-15	-7	+1
試驗二	安慰劑	226	+1	+1	-1	+2	-2
	EZETROL	666	-12	-18	-16	-9	+1
兩試驗的綜合資料	安慰劑	431	0	+1	-2	0	-2
	EZETROL	1288	-13	-18	-16	-8	+1

[a] 與治療前基礎值的差異百分比中數

併用 Statin 類藥品

EZETROL 與 Statin 類藥品合併服用

在四個為期十二週、多中心、雙盲性，並以安慰劑為對照的研究中，1187 位高膽固醇血症患者分別接受 EZETROL 10 mg 單方，或合併以不同劑量的 atorvastatin、simvastatin、pravastatin 或 lovastatin 治療。結果顯示，降低 LDL-C 的效果並不受各 statin 類藥品及不同使用劑量的影響。此外，以最低劑量(10 mg)的 EZETROL 併用任何一種 statin 類藥品所達到的降低 LDL-C 的效果相近或優於單方使用最高劑量的 statin 類藥品(請參見表二)。

表二： 服用 EZETROL 與 Statin 類藥品試驗前後的 LDL-C 血中濃度計算值平均差異百分比

	Atorvastatin Study	Simvastatin Study	Pravastatin Study	Lovastatin Study
安慰劑	+4	-1	-1	0
EZETROL	-20	-19	-20	-19
10 mg statin	-37	-27	-21	-20
EZETROL + 10 mg statin	-53	-46	-34	-34
20 mg statin	-42	-36	-23	-26
EZETROL + 20 mg statin	-54	-46	-40	-41
40 mg statin	-45	-38	-31	-30
EZETROL + 40 mg statin	-56	-56	-42	-46
80 mg statin	-54	-45	-	-
EZETROL + 80	-61	-58	-	-

mg statin				
statin 各種劑量結果綜合	-44	-36	-25	-25
EZETROL + statin 各種劑量結果綜合	-56	-51	-39	-40

綜合分析服用 EZETROL 及併用各種劑量的 statin 類藥品的結果顯示，EZETROL 有益於調節 total-C、Apo B、TG 及 HDL-C 的功效(請參見表三)。

表三：綜合分析 Total-C、ApoB、TG 及 HDL-C 試驗前後差異的平均百分比

	Total-C	Apo B	TG[a]	HDL-C
EZETROL + Atorvastatin	-41	-45	-33	+7
Atorvastatin 單方	-32	-36	-24	+4
EZETROL + Simvastatin	-37	-41	-29	+9
Simvastatin 單方	-26	-30	-20	+7
EZETROL + Pravastatin	-27	-30	-21	+8
Pravastatin 單方	-17	-20	-14	+7
EZETROL + Lovastatin	-29	-33	-25	+9
Lovastatin 單方	-18	-21	-12	+4

[a] 差異百分比中數

已服用 Statin 類藥品治療期間再合併服用 EZETROL

一項為期八週、多中心、雙盲性、以安慰劑為對照的試驗中，接受單方 statin 類藥品治療後，LDL-C 仍未降低至國際膽固醇衛教計畫(National Cholesterol Education Program; NCEP)目標(100-160 mg/dl，視試驗前狀況而定)的 769 位高膽固醇血症患者，以隨機方式分組，除繼續服用 statin 類藥品外，合併服用 EZETROL10 mg 或安慰劑。

這些接受單方statin類藥品治療而在試驗進行前LDL-C未降至目標值的病人約佔 82%；於試驗結束後達LDL-C目標的，接受EZETROL治療的有 72 %，而接受安慰劑的僅 19 %。

試驗結果顯示，已服用 statin 類藥品治療期間再合併服用 EZETROL，顯著地比安慰劑可降低 total-C、LDL-C、Apo B 及 TG，同時可提高 HDL-C(請參見表四)。而任何一種 statin 類藥品降低 LDL-C 的效果都一樣。

表四：高膽固醇血症病人以statin類藥品治療[a]期間再合併服用EZETROL 的平均效果(與試驗前基礎值的差異平均值百分比)

治療方式 (每日劑量)	人數	Total-C	LDL-C	Apo B	TG[b]	HDL-C
服用中的 Statin 藥品+安慰劑	390	-2	-4 (-6 mg/dl[c])	-3	-3	+1
服用中的 Statin 藥品+EZETROL	379	-17	-25 (-36 mg/dl[c])	-19	-14	+3

[a] 接受各種statin藥品的病患比率 40% atorvastatin，31% simvastatin，29%其他 (pravastatin、fluvastatin、cerivastatin、lovastatin)

[b] 與基礎值比較的差異百分比中數

[c] 與試驗前LDL-C基礎值(statin + EZETROL :138 mg/dl及statin + placebo :139 mg/dl)的差異值。

EZETROL 或安慰劑加入 statin 類藥品治療後，降低 C-reactive protein 的中數分別為 10 %及 0 %。

一項多中心，雙盲、為期十四週的試驗中，621 位高膽固醇血症的病人，每天服用 atorvastatin 10 mg，病患 LDL-C 基礎值為 > 130 mg/dl，以隨機分組，分別服用 atorvastatin 20 mg 或在 atorvastatin 10 mg 之外合併服用 EZETROL 10 mg。若病患的 LDL-C 未達目標值(< 100 mg/dl)，服用單方 atorvastatin 的病患組可視情況將劑量調高至 80 mg，而合併服用 EZETROL 組的病患可將 atorvastatin 的劑量調高至 40 mg。試驗前 LDL-C 的平均基礎值為 187 mg/dl，並且約有 60 %的病人患有異型接合子家族性高膽固醇血症(HeFH)。試驗結束時，兩組達到 LDL-C 目標值的病患數有顯著的差異，分別是併用 EZETROL 組有 22 %，而單方 atorvastatin 組為 7 %。試驗進行四週時，LDL-C 值的降低效果就有明顯的差異，即合併服用 EZETROL 及 atorvastatin 10 mg 的有 24 %，服用 atorvastatin 20 mg 為 9 %。患有 HeFH 的病人也達到類似的 LDL-C 目標達成率及 LDL-C 降低值。

另一個類似的試驗，針對 100 位正接受 simvastatin 20 mg 治療而未達 LDL-C 目標值的高膽固醇血症病人，再增加simvastatin 劑量或調高劑量且合併服用 EZETROL 10 mg 之後所得療效與前述 atorvastatin 試驗結果相似。即兩組間達到 LDL-C 目標值的病患數(EZETROL 合併服用 simvastatin 組有 27 %，simvastatin 單方組僅 3 %)及 LDL-C 值的降低效果(EZETROL 併服 simvastatin 組降低 24 %，simvastatin 單方組降低 11 %)具有明顯的差異。

併用 Fenofibrate

一項多中心、雙盲性、以安慰劑為對照在混合性高膽固醇患者所進行的研究中，有 625 位患者接受治療達 12 週及 576 位患者達一年。以隨機的方式讓病患接受安慰劑、EZETROL 單方、160 mg fenofibrate 單方或者 EZETROL 合併 160 mg fenofibrate。

EZETROL 合併 fenofibrate 和單獨投與 fenofibrate 比較，可顯著降低 total-C、LDL-C、Apo B 以及 non-HDL-C。合併使用 EZETROL 和 fenofibrate 其降低 TG 和提升 HDL-C 的百分比和單獨服用 fenofibrate 是相當的(請參見表五)

表五：混合性高膽固醇患者同時開始服用EZETROL和fenofibrate的反應 (第 12 週與治療前基礎值[b]差異的平均百分比[a])

治療方式 (每日劑量)	人數	Total-C	LDL-C	ApoB	TG[a]	HDL-C	Non-HDL-C
安慰劑	63	0	0	-1	-9	+ 3	0
EZETROL	185	-12	-13	-11	-11	+ 4	-15
Fenofibrate 160 mg	188	-11	-6	-15	-43	+ 19	-16
EZETROL+ Fenofibrate 160mg	183	-22	-20	-26	-44	+ 19	-30

[a] 三酸甘油酯與基礎值比較的平均百分比

[b] 基礎值-未投與降血脂藥品

治療一年後其血脂指標的改善與 12 週的結果一致(如上表)。

同型接合子家族性高膽固醇血症

一項為期十二週，雙盲、隨機性的試驗，用於評估 EZETROL 對治療 HoFH 的效果，收錄了 50 位正接受 40 mg 的 atorvastatin 或 simvastatin 治療、無論是否併用 LDL apheresis，經臨床或基因型診斷為 HoFH 的病人，經隨機分成三組，分別接受 80 mg 的 atorvastatin 或 simvastatin、合併服用 EZETROL10 mg 及 40 mg 的 atorvastatin 或 simvastatin 或合併服用 EZETROL 10 mg 及 80 mg 的 atorvastatin 或 simvastatin。結果如表六所示，合併服用 EZETROL10 mg 及 40 mg 或 80 mg 的 atorvastatin 或 simvastatin 比服用單方 40 mg 或 80 mg 的 atorvastatin 或 simvastatin 更顯著地降低 LDL-C。

表六：HoFH 病人以 EZETROL 治療的平均效果(與試驗前基礎值的差異平均值百分比)

治療方式 (每日劑量)	人數	LDL-C
Atorvastatin (80 mg) 或 Simvastatin (80 mg)	17	-7
EZETROL 合併服用 Atorvastatin (40, 80 mg) 或 Simvastatin (40, 80 mg)	33	-21
分組分析 EZETROL 合併服用 Atorvastatin (80 mg) 或 Simvastatin (80 mg)	17	-27

同型接合子性麥硬脂醇血症(植物脂醇血症)

另有一項藉以評估 EZETROL 治療同型接合子性麥硬脂醇血症效果的試驗。在這個為期八週、多中心、雙盲、對照以安慰劑，收錄 37 位同型接合子性麥硬脂醇血症患者，以隨機方式分組，30 位以 EZETROL10 mg 治療，其餘 7 位接受安慰劑。結果顯示，EZETROL 可以顯著地降低兩個主要的植物脂醇值，sitosterol 及 campesterol，分別降低了 21 %及 24 %。相對的，服用安慰劑的病人的 sitosterol 及 campesterol 則分別升高了 4 % 及 3 %。試驗中，以 EZETROL 治療的病人，其降低植物脂醇的效果不斷的有進展。

試驗結果顯示，無論 EZETROL 併服降膽酸藥物(bile acid sequestrants) (n=8)或未併服(n=21)，所得的效果都一樣。

適應症

高膽固醇血症、同型接合子性麥硬脂醇血症(植物脂醇血症)。

說明

原發性高膽固醇血症(Primary Hypercholesterolemia)：

【說明】EZETROL 單獨投與，或與 HMG-CoA 還原酶抑制劑(statin)合併投與，用於治療原發性高膽固醇血症(異型接合子家族性及非家族性)的病人，配合飲食控制，可以降低總膽固醇(total cholesterol; total-C)、低密度脂蛋白膽固醇(low-density lipoprotein cholesterol; LDL-C)、apolipoprotein B (Apo B)，以及三酸甘油酯(triglycerides; TG)，並增加高密度脂蛋白膽固醇。

同型接合子家族性高膽固醇血症(Homozygous Familial Hypercholesterolemia，簡稱HoFH)：

【說明】EZETROL 與 Statin 類藥品合併投與於同型接合子家族性高膽固醇血症的病人，可以降低總膽固醇、低密度脂蛋白膽固醇的濃度。病人可同時接受輔助治療(如：LDL 血漿分離術)。

同型接合子性麥硬脂醇血症(植物脂醇血症)(Homozygous Sitosterolemia，又稱 Phytosterolemia)：

【說明】EZETROL 可用於同型接合子家族性麥硬脂醇血症的病人，可以降低麥硬脂醇(sitosterol)以及 campesterol 的濃度。

用法、用量

病人應該接受適當的降膽固醇飲食控制，並且在 EZETROL 治療期間仍需持續飲食控制。

EZETROL 的建議劑量為 10 毫克，每天服用一次，單獨投與或與 statin 類藥品合併投與。EZETROL 可以在一天中的任何時候服用，隨餐或空腹均可。

腎臟功能受損

單一療法

用於腎臟功能受損患者時，不需要調整 EZETROL 的劑量(請參見病人特性「特

殊族群」)。

併用 Simvastatin 療法

在腎功能不全的病人不需要調整 EZETROL 的劑量。用於中度及輕度腎功能不全患者時，不需調整 simvastatin 的劑量。對於嚴重腎功能不全的患者(肌酸酐廓清率<30ml/min)，simvastatin 超過 10 mg/day 以上的劑量都應審慎考慮。如果認為有必要使用時，應謹慎服藥(請參見 simvastatin 仿單)。

老人

老年人不需要調整劑量(請參見病人特性「特殊族群」)。

兒童

用於大於十歲的兒童及青少年：不需要調整劑量(請參見病人特性「特殊族群」)。十歲以下的兒童：不建議使用 EZETROL。

肝功能不全

在輕微肝功能不全的病人(Child Pugh score 5 to 6)不需要調整劑量。但是在中度(Child Pugh score 7 to 9)或重度肝功能不全(Child Pugh score > 9)的病人不建議使用 EZETROL(請參見注意事項和病人特性「特殊族群」)。

合併服用降膽酸藥物

EZETROL 合併服用降膽酸藥物時，服用 EZETROL 之後，必須間隔兩小時以上才能服用降膽酸藥物，或服用降膽酸藥物之後，必須間隔四小時以上才能服用 EZETROL。

禁忌症

對本藥的任何成分過敏。

當 EZETROL 合併服用 statin 類或 fenofibrate 藥物時，請參考該藥物的仿單使用。

注意事項

當 EZETROL 與 statin 類或 fenofibrate 藥物合併投與時，請參考該藥品的仿單。

肝酵素

在一項有對照組的臨床試驗中，觀察同時服用 EZETROL 與 statin 類藥品病人，曾發生氨基轉移酵素持續升高的情形(比 ULN 正常值上限大三倍以上)。因此，當 EZETROL 與 statin 類藥品合併使用時，在治療初期應做肝功能檢查，同時也要依照該 statin 類藥品的建議做肝功能檢查(請參見副作用)。

在一項超過 9000 位慢性腎臟疾病病人且有對照組的臨床試驗中，病人經隨機分配接受 EZETROL 10 mg 併用 simvastatin 20 mg，1 天 1 次(n=4650)或安慰劑(n=4620)的治療(追蹤期中位數為 4.9 年)。EZETROL 併用 simvastatin 的氨基轉移酵素持續升高(比正常值上限大三倍以上)發生率為 0.7%，而安慰劑組為 0.6%(請參見副作用)。

骨骼肌

於多項臨床試驗中得知，與 EZETROL 有關的肌病變或橫紋肌溶解症，和相關控制組(安慰劑或單獨使用 statin 類藥品)作比較，沒有過量表現。然而，肌病變與橫紋肌溶解症是 statin 類藥品及降血脂藥物，已知的不良反應。多項臨床試驗中顯示，CPK 大於十倍的正常值上限，於使用 EZETROL 時，發生率為 0.2%，於使用安慰劑時，發生率為 0.1%，同時使用 EZETROL 與 statin 類藥品時，發生率為 0.1%，單獨使用 statin 類藥品時，發生率為 0.4%。

EZETROL 上市後經驗中，不論其相關性，有通報肌病變及橫紋肌溶解症不良反應的案例。大部分橫紋肌溶解症的病患，是發生於開始服用 EZETROL 前使用 statin 類藥品。然而，於 EZETROL 單一療法中，極少通報橫紋肌溶解症的案例，當併用 EZETROL 於已知會增加橫紋肌溶解症風險的製劑時，也極少通報橫紋肌溶解症的案例。所有的病患於開始服用 EZETROL 時，應被告知有肌病變的風險及當發生任何不預期的肌肉痛、觸痛、虛弱無力，應立即回報。同時服用 EZETROL 及任何 statin 類藥品的病患，若被診斷出或懷疑有肌病變時，應立即停用。肌病變意指發生上述症狀及肌酸磷酸肌酶大於十倍的正常值上限。

在一項超過 9000 位慢性腎臟疾病病人的臨床試驗中，病人經隨機接受 EZETROL 10 mg 併用 simvastatin 20 mg，1 天 1 次(n=4650)或安慰劑(n=4620)的治療(追蹤期中位數為 4.9 年)。EZETROL 併用 simvastatin 的肌病變/橫紋肌溶解症發生率為 0.2%，而安慰劑組為 0.1% (請參見副作用)。

肝功能不全

在中度或重度肝功能不全的病人，因為並不清楚 ezetimibe 的使用會造成何種影響，所以，EZETROL 並不建議使用於這一群病人(請參見病人特性「特殊族群」)。

Fibrates

Ezetimibe 和除 fenofibrate 外的 fibrates 合併使用的安全性和有效性尚未建立，因此，並不建議 EZETROL 和除 fenofibrate 外的 fibrates 合併使用(請參見藥物交互作用)。

Fenofibrate

假如併用 EZETROL 和 fenofibrate 的患者懷疑患有膽石症，則必須作膽囊相關檢查且應該考慮改變降血脂的治療(請參見副作用及 fenofibrate 的仿單)

Cyclosporine

考慮合併使用 ezetimibe 與 cyclosporine 時，必須謹慎評估。同時服用 EZETROL 及 cyclosporine 時，需監控 cyclosporine 濃度(請參見藥物交互作用)。

抗凝血劑

若併用 EZETROL 於 warfarin、其它 coumarin 類抗凝血劑或 fluindione 療程時，應適當地監控國際標準比值(International Normalized Ratio, INR) (請參見藥物交互作用)。

懷孕

目前尚無適當和控制良好的試驗來研究懷孕婦女服用 ezetimibe 的影響。在懷孕期間，只有當潛在的利益大於對胎兒的風險，才可以服用 ezetimibe。

於器官形成階段的大鼠和兔子經口投予 ezetimibe，檢視其對胚胎發展之影響的研究結果顯示，在 250 或 500 或 1000 mg / 公斤 / 天的試驗劑量下，並未顯示有胚胎致死作用。投予大鼠 1000 mg / 公斤 / 天的劑量(相當於人類每天服用 10 mg 時、其總 ezetimibe 的 AUC 0-24 小時的十倍)，觀察到胎兒骨骼畸形現象(多長一對的胸肋骨，頸椎骨中心未骨化，肋骨短縮)的發生率增加。投予兔子 1000 mg / 公斤 / 天的劑量(相當於人類每天服用 10 mg 時、其總 ezetimibe 的 AUC 0-24 小時的 150 倍)，觀察到增長多餘的胸肋骨發生率增加。當懷孕的大鼠和兔子經口投予多劑量的時候，ezetimibe 會進入胎盤。

對器官形成階段的大鼠和兔子投與多劑量的 ezetimibe 和 HMG-CoA 還原酶抑制劑(statins)，結果導致體內有較高濃度的 ezetimibe 及 statins。與 ezetimibe 單方相較，於複方時所使用的 ezetimibe 於較低劑量時便產生生殖方面的影響。

所有的 HMG-CoA 還原酶抑制劑均禁用於孕婦和授乳婦女。當有懷孕可能的婦女在併服 ezetimibe 與 HMG-CoA 還原酶抑制劑之前，應該先參考 HMG-CoA 還原酶抑制劑的懷孕使用分級與使用說明書。

分娩

目前尚未知道 ezetimibe 對懷孕婦女分娩時是否有任何的影響。

哺乳婦女

在老鼠實驗中發現 ezetimibe 會分泌到乳汁中，但是是否會分泌到人類的乳汁則不明。因此，除非潛在的效益會大於對嬰兒潛在的危險，否則哺乳婦女不應使用 EZETROL。

藥物交互作用

臨床前試驗發現，ezetimibe 並不會誘發 cytochrome P450 藥物代謝酵素。Ezetimibe 和已知經由 cytochrome P450 1A2、2D6、2C8、2C9、3A4，或是 N-Acetyltransferase 代謝的藥物，在臨床上並沒有觀察到明顯的藥動學交互作用。Ezetimibe 和 dapsone、dextromethorphan、digoxin、口服避孕藥(ethinyl estradiol 和 levonorgestrel)、glipizide、tolbutamide、midazolam 合併投與時，對於這些藥品的藥動學沒有影響。Cimetidine 和 ezetimibe 一起使用時，對 ezetimibe 的生體可用率沒有影響。

制酸劑

和制酸劑合併投與，會降低 ezetimibe 的吸收速率，但不影響 ezetimibe 的生體可用率。吸收速率的降低並無臨床上的意義。

Cholestyramine

和 cholestyramine 合併投與時，總 ezetimibe(ezetimibe + ezetimibe glucuronide)的 AUC 平均值會降低約 55%。Ezetimibe 和 cholestyramine 合併投與所增加降低 LDL-C 的作用會因此減弱。

Cyclosporine

在一項試驗中，有八位病人在腎臟移植後，肌酸酐廓清率>50 mL/min，且服用固定劑量的cyclosporine，在服用單一劑ezetimibe 10 mg之後，結果造成總ezetimibe的AUC平均值為另一試驗中 17 位健康受試者的 3.4 倍(涵蓋 2.3 倍至 7.9 倍)。另外一項試驗中，一位腎臟移植的嚴重腎功能不全患者(肌酸酐廓清率為 13.2 mL/min/1.73 m^2)，接受包括cyclosporine在內的多種藥物治療，結果這位病人的總ezetimibe的AUC比對照組大了 12 倍之多。在一項之兩階段交叉試驗，12 位健康受試者，每天服用ezetimibe 20 mg，為期 8 天，並於第 7 天服用單一劑量 cyclosporine 100 mg，其cyclosporine AUC比單獨服用單一劑量cyclosporine 100 mg，平均上升 15 % (範圍從下降 10 %至上升 51 %)(請參見注意事項)。

Fibrates

Ezetimibe 和 fenofibrate 併用的安全性及療效已經由臨床試驗評估(請參見副作用和臨床試驗，併用 Fenofibrate)，和其他 fibrates 類藥品合併使用的安全性和有效性則尚未建立。Fibrates 可能會增加膽固醇分泌至膽汁中的量，因而導致膽石病(cholelithiasis)。臨床前試驗中發現，ezetimibe 會使狗膽汁中的膽固醇增加，這項作用對人體的關聯性仍未知，因此，在完成相關人體試驗之前，不建議併用 ezetimibe 和除 fenofibrate 外的 fibrates。

Fenofibrate

藥物動力學試驗顯示，和 fenofibrate 合併投與時增加 total ezetimibe 的濃度約 1.5 倍，此增加被認為不具臨床意義。

Gemfibrozil

藥物動力學試驗顯示，和 gemfibrozil 合併投與時增加 total ezetimibe 的濃度約 1.7 倍，此增加被認為不具臨床意義。目前尚無臨床試驗數據。

Statins

Ezetimibe 與 atorvastatin、simvastatin、pravastatin、lovastatin、fluvastatin、rosuvastatin 合併投與時，在臨床上並沒有觀察到明顯的藥動學交互作用。

抗凝血劑

於一項試驗中，12 位健康成人男性受試者同時服用 warfarin 與 ezetimibe(一天一次，每次 10 mg)，對於 warfarin 的生體可用率及前凝血酶原時間並無有意義的影響。曾有上市後報告指出併用 EZETROL 於 warfarin 或 fluindione 療程中的病患，其國際標準比值有上升的情形，其中大多數病患，當時也正在使用其他藥物治療(請參見注意事項)。

副作用

臨床試驗為期最多 112 週，每日單獨投與 EZETROL 10 mg (n=2396)或併用 statin 類藥品(n=11,308)或 fenofibrate (n=185)顯示，EZETROL 具有良好的耐受性，產

生的不良反應多為輕微而短暫。服用 EZETROL 的副作用總發生率與安慰劑類似，因為不良反應而需要停藥的機率也與安慰劑類似。
單獨使用 EZETROL 的病人(n=2396)，其不良反應發生率高於安慰劑組的病人(n=1159)，或併用 statin 類藥品的病人(n=11,308)，其不良反應發生率高於單獨使用 statin 的病人(n=9361)，所發生與藥品相關且常見(發生率≧ 1/100，< 1/10)或罕見(發生率≧ 1/1,000，< 1/100)之不良反應如下所列。
EZETROL 單獨使用：
實驗室數值：
罕見：ALT 及/或 AST 值上升、血液 CPK 增加、gamma-麩胺醯轉移酶(gamma-glutamyltransferase)增加、肝功能檢驗異常。
呼吸道、胸部及橫隔膜異常：
罕見：咳嗽
胃腸道異常：
常見：腹痛、腹瀉、脹氣
罕見：消化不良、胃食道逆流、噁心
肌肉骨骼及結締組織異常：
罕見：關節痛、肌肉痙攣、頸痛
代謝及營養異常：
罕見：食慾降低
血管異常：
罕見：熱潮紅、高血壓
一般及投與部位：
常見：疲勞
罕見：胸痛、疼痛
EZETROL 與 statin 類藥品合併使用：
實驗室數值：
常見：ALT 及/或 AST 值上升
神經系統異常：
常見：頭痛
罕見：皮膚感覺異常
胃腸道異常：
罕見：口乾、胃炎
皮膚及皮下組織異常：
罕見：搔癢、紅疹、蕁麻疹
肌肉骨骼及結締組織異常：
常見：肌痛
罕見：背痛、肌肉無力、四肢疼痛
一般及投與部位：
罕見：無力、周邊水腫
EZETROL 與 fenofibrate 合併使用：
胃腸道異常：
常見：腹痛
一項多中心、雙盲、以安慰劑為對照組在混合性高膽固醇血症患者所進行的研究中，有 625 位患者接受治療達 12 週及 576 位患者達一年。此試驗未在治療組針對罕見事件進行比較。發生臨床上具重要意義的氨基轉移酵素升高(持續大於三倍的正常值上限)的發生率(95%的信賴區間)，在單獨使用 fenofibrate 與 EZETROL 合併使用 fenofibrate 的患者分別為 4.5%(1.9，8.8)與 2.7%(1.2，5.4)。同樣地，單獨使用 fenofibrate 與 EZETROL 合併使用 fenofibrate 發生膽囊切除的比例分別為 0.6%(0.0，3.1)與 1.7%(0.6，4.0)(請參見注意事項)。此試驗在每個治療組中並沒有發生 CPK 大於十倍正常值上限的情形。

慢性腎臟疾病病人

在一超過 9000 位病人的心臟與腎臟保護試驗(SHARP)中，病人接受固定劑量的 EZETROL 10 mg 併用 simvastatin 20 mg，1 天 1 次(n=4650)或安慰劑(n=4620)的治療。追蹤期中位數為 4.9 年。該試驗僅記錄嚴重不良反應事件，以及因為任何嚴重不良反應事件而退出試驗的資料。因為不良反應事件而退出試驗的比例，彼此相當(接受 EZETROL 併用 simvastatin 治療的病人有 10.4%，而接受安慰劑治療的病人有 9.8%)。肌病變/橫紋肌溶解症的發生率方面，接受 EZETROL 併用 simvastatin 治療的病人有 0.2%，而接受安慰劑治療的病人有 0.1%。氨基轉移酵素持續升高(比正常值上限大三倍以上)方面，接受 EZETROL 併用 simvastatin 治療的病人有 0.7%，而接受安慰劑治療的病人有 0.6%。該試驗在事先定義的不良反應事件方面，包括癌症(EZETROL 併用 simvastatin 治療組 9.4%，安慰劑組 9.5%)、肝炎、膽囊切除或膽結石/胰臟炎的併發症，其發生率並未出現具有統計上顯著的增加。

實驗室數值

在有對照組且只使用單一藥品治療的臨床試驗中，發生臨床上具有重要意義的氨基轉移酵素升高(持續 ALT 及/或 AST≧ 三倍的正常值上限)的發生率，單獨使用 EZETROL 的病人(0.5%)與使用安慰劑的病人類似(0.3%)。而在合併兩種藥品治療的臨床試驗中，病人同時服用 EZETROL 與 statin 類藥品的發生率為 1.3%，單獨服用 statin 的病人則為 0.4%。這些數值的升高通常是沒有症狀的，與膽汁鬱積無關，停藥或不停藥都會回到治療前的數值(請參見注意事項)。
單獨使用 EZETROL 的病人和與 statin 類藥品合併投與的病人，發生臨床上有意義的 CPK(≧ 十倍的正常值上限)數值升高的情形，分別與使用安慰劑和單獨使用 statin 的病人類似。

上市後經驗

上市後經通報的不良反應經驗，不論其相關性評估如下：
血液及淋巴系統異常：血小板減少症
神經系統異常：頭暈、皮膚感覺異常
胃腸道異常：胰臟炎、便秘
皮膚及皮下組織異常：多形性紅斑
肌肉骨骼及結締組織異常：肌痛、肌病變/橫紋肌溶解症(請參見注意事項)
一般及投與部位：無力
免疫系統異常：包含休克性敏感反應、血管神經性水腫、皮疹及蕁麻疹的過敏反應
肝膽異常：肝炎、膽石症、膽囊炎
精神異常：抑鬱

過量服用

針對 15 位健康受試者，每日投與 ezetimibe 50 mg 長達 14 天，18 位原發性高膽固醇血症的病人，每日投予 ezetimibe 40 mg 長達 56 天，及 27 位豆固醇血症的病人，每日投予 40 mg 長達 26 週，臨床研究結果顯示，其一般而言具有良好的耐受性。
曾有少數幾例過量使用本品的紀錄，其中多半無副作用產生，發生副作用的也都不嚴重。若發生過量服用的情形時，應該給予病人症狀及支持性治療。

儲存

儲存溫度為 30℃(86°F)以下，併防潮濕。

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WPC-MK0653-T-112011
0653-TWN-2012-005310V1

Tablets
EZETROL®
(ezetimibe)

ACTIVE INGREDIENTS

Each tablet of EZETROL for oral administration contains 10 mg ezetimibe.

THERAPEUTIC CLASS

EZETROL® (ezetimibe) is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols.

MECHANISM OF ACTION

EZETROL is orally active and potent, with a unique 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 localizes 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. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins). 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 the fat soluble vitamins A and D. While, in toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors was seen in rats, dogs, and rabbits, no clinically significant pharmacokinetic interactions were seen in humans when ezetimibe was co-administered with HMG-CoA reductase inhibitors (see DRUG INTERACTIONS)."

In a 2-week clinical study in 18 hypercholesterolemic patients, EZETROL inhibited intestinal cholesterol absorption by 54 %, compared with placebo. By inhibiting the absorption of intestinal cholesterol, ezetimibe reduces the delivery of cholesterol to the liver. Statins reduce cholesterol synthesis in the liver. Together these distinct mechanisms provide complementary cholesterol reduction. EZETROL, administered with a statin, reduces total-C, LDL-C, Apo B, and TG and increases HDL-C in patients with hypercholesterolemia, beyond either treatment alone. Administration of EZETROL with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, TG, HDL-C, and non-HDL-C in patients with mixed hyperlipidemia.

Clinical studies demonstrate that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

PHARMACOKINETICS

Absorption

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as EZETROL 10-mg tablets. EZETROL can be administered with or without food.

Distribution

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

Metabolism

Ezetimibe is metabolized 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.

Elimination

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 feces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Characteristics in Patients (Special Populations)

Pediatric 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 pediatric population < 10 years of age are not available.

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 young subjects treated with EZETROL. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (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 PRECAUTIONS).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl □ 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

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

Gender

Plasma concentrations for total ezetimibe are slightly higher (< 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Race

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

CLINICAL STUDIES

Primary Hypercholesterolemia

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, EZETROL 10 mg significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex, race, and baseline LDL-C. In addition, EZETROL had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, had no effect on prothrombin time, and did not impair adrenocortical steroid hormone production.

Table 1: Mean Response to EZETROL in Patients with Primary Hypercholesterolemia (Mean % Change from Baseline)

	Treatment group	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Study 1	Placebo	205	+1	+1	-1	-1	-1
	EZETROL	622	-12	-18	-15	-7	+1
Study 2	Placebo	226	+1	+1	-1	+2	-2
	EZETROL	666	-12	-18	-16	-9	+1
Pooled Data (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	EZETROL	1288	-13	-18	-16	-8	+1

[a] Median % change from baseline

Co-Administration with a Statin

EZETROL Initiated Concurrently with a Statin

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 1187 patients with hypercholesterolemia, EZETROL 10 mg was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin. In general, the incremental effect on LDL-C reduction was independent of the dose or specific statin used. In addition, LDL-C reduction for EZETROL co-administered with the lowest tested dose (10 mg) of any of the statins was similar to or greater than the LDL-C reduction of the highest tested dose of the corresponding statin administered alone (Table 2).

Table 2: Mean % Change from Baseline in Plasma Concentration of Calculated LDL-C for EZETROL Administered with Statins

	Atorvastatin Study	Simvastatin Study	Pravastatin Study	Lovastatin Study
Placebo	+4	-1	-1	0
EZETROL	-20	-19	-20	-19
10 mg statin	-37	-27	-21	-20
EZETROL + 10 mg statin	-53	-46	-34	-34
20 mg statin	-42	-36	-23	-26
EZETROL + 20 mg	-54	-46	-40	-41

statin				
40 mg statin	-45	-38	-31	-30
EZETROL + 40 mg statin	-56	-56	-42	-46
80 mg statin	-54	-45	-	-
EZETROL + 80 mg statin	-61	-58	-	-
Pooled data: All statin doses	-44	-36	-25	-25
Pooled data: All EZETROL + statin doses	-56	-51	-39	-40

In a pooled analysis of all EZETROL + statin doses, EZETROL had a beneficial effect on total-C, Apo B, TG, and HDL-C (Table 3).

Table 3: Pooled Analysis of the Mean % Change from Baseline in Total-C, ApoB, TG, and HDL-C

	Total-C	**Apo B**	**TG[a]**	**HDL-C**
EZETROL + Atorvastatin	-41	-45	-33	+7
Atorvastatin alone	-32	-36	-24	+4
EZETROL + Simvastatin	-37	-41	-29	+9
Simvastatin alone	-26	-30	-20	+7
EZETROL + Pravastatin	-27	-30	-21	+8
Pravastatin alone	-17	-20	-14	+7
EZETROL + Lovastatin	-29	-33	-25	+9
Lovastatin alone	-18	-21	-12	+4

[a] median % change

EZETROL Added to On-going Statin Therapy

In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (100 to 160 mg/dl, depending on baseline characteristics) were randomized to receive either EZETROL 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82 %), LDL-C goal at study endpoint was achieved by 72 % and 19 % of patients randomized to EZETROL and placebo, respectively.

EZETROL, added to on-going statin therapy, significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C, compared with placebo (Table 4). LDL-C reductions were consistent across all statins.

Table 4: Mean Response to Addition of EZETROL to On-going Statin Therapy[a] in Patients with Hypercholesterolemia (Mean % Change from Baseline)

Treatment (Daily Dose)	**N**	**Total-C**	**LDL-C**	**Apo B**	**TG[b]**	**HDL-C**
On-going Statin +Placebo	390	-2	-4 (-6 mg/dl [c])	-3	-3	+1
On-going Statin +EZETROL	379	-17	-25 (-36 mg/dl[c])	-19	-14	+3

[a] Percentages of patients receiving each statin: 40% atorvastatin , 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)

[b] Median % change from baseline

[c] Change in LDL-C from baseline LDL-C (138 mg/dl and 139 mg/dl for statin + EZETROL and statin + placebo, respectively)

EZETROL or placebo added to statin therapy reduced median C-reactive protein by 10 % or 0 % from baseline, respectively.

In a multicenter, double-blind, 14 week study, 621 patients with hypercholesterolemia receiving atorvastatin 10 mg daily with an LDL-C > 130 mg/dl were randomized to receive atorvastatin 20 mg or EZETROL 10 mg added to atorvastatin 10 mg therapy. The atorvastatin dose could be titrated up to 80 mg in the atorvastatin arm and up to 40 mg in the EZETROL plus atorvastatin co-administration arm, based on patients not attaining LDL-C goal (< 100 mg/dl). The mean baseline LDL-C was 187 mg/dl and approximately 60 % of the patients had heterozygous familial hypercholesterolemia (HeFH). At study end, there was a significant difference in attainment of LDL-C goal between patients in the EZETROL co-administration arm (22 %) and patients on atorvastatin monotherapy (7 %). At week 4, there was a significant difference in LDL-C reductions between co-administration patients (24 %; EZETROL + atorvastatin 10 mg) and monotherapy patients (9 %; atorvastatin 20 mg). In the sub-group of patients with HeFH, similar results for LDL-C goal attainment and LDL-C reductions were achieved.

In a similarly designed study in 100 patients with hypercholesterolemia receiving simvastatin 20 mg and not at LDL-C goal, the addition of EZETROL 10 mg to simvastatin titration compared to titration of simvastatin alone produced similar advantages to those observed in the atorvastatin study described above. For example, significant differences in LDL-C goal attainment (27 % for EZETROL + simvastatin vs. 3 % for simvastatin alone) and LDL-C reductions (24 % for EZETROL + simvastatin vs. 11 % for simvastatin alone) were achieved.

Co-administration with Fenofibrate

In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to 1 year. Patients were randomized to receive placebo, EZETROL alone, 160 mg fenofibrate alone, or EZETROL and 160 mg fenofibrate.

EZETROL co-administered with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate administered alone. The percent decrease in TG and percent increase in HDL-C for EZETROL co-administered with fenofibrate were comparable to those for fenofibrate administered alone (see Table 5).

Table 5: Response to EZETROL and Fenofibrate Initiated Concurrently in Patients with Mixed Hyperlipidemia (Mean[a] % Change from Untreated Baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
Placebo	63	0	0	-1	-9	+3	0
EZETROL	185	-12	-13	-11	-11	+4	-15
Fenofibrate 160 mg	188	-11	-6	-15	-43	+19	-16
EZETROL + Fenofibrate 160 mg	183	-22	-20	-26	-44	+19	-30

[a] For triglycerides, median % change from baseline

[b] Baseline - on no lipid-lowering drug

Improvements in lipid endpoints after 1 year of treatment were consistent with the 12-week data displayed above.

Homozygous Familial Hypercholesterolemia (HoFH)

A study was conducted to assess the efficacy of EZETROL in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), EZETROL 10 mg administered with atorvastatin or simvastatin (40 mg), or EZETROL 10 mg administered with atorvastatin or simvastatin (80 mg). Results are shown in Table 6. EZETROL, administered with atorvastatin (40 or 80 mg) or simvastatin (40 or 80 mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg.

Table 6: Mean Response to EZETROL in Patients with HoFH (Mean % Change from Baseline)

Treatment (Daily Dose)	N	LDL-C
Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-7
EZETROL + Atorvastatin (40, 80 mg) or Simvastatin (40, 80 mg)	33	-21
Sub-group analysis: EZETROL + Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-27

Homozygous Sitosterolemia (Phytosterolemia)

A study was conducted to assess the efficacy of EZETROL in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolemia were randomized to receive EZETROL 10 mg (n=30) or placebo (n=7). EZETROL significantly lowered the two major plant sterols, sitosterol and campesterol, by 21 % and 24 % from baseline, respectively. In contrast, patients who received placebo had increases in sitosterol and campesterol of 4 % and 3 % from baseline, respectively. For patients treated with EZETROL, the reduction in plant sterols was progressive over the course of the study.

Reductions in sitosterol and campesterol were consistent between patients taking EZETROL concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

INDICATIONS SUMMARY

Hypercholesterolemia, homozygous sitosterolemia (phytosterolemia)

INDICATIONS DESCRIPTION

Primary Hypercholesterolemia

EZETROL, administered with an HMG-CoA reductase inhibitor (statin) or alone, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HoFH)

EZETROL, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Homozygous Sitosterolemia (Phytosterolemia)

EZETROL is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

DOSAGE AND ADMINISTRATION

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with EZETROL.

The recommended dose of EZETROL is 10 mg once daily, used alone or with a statin. EZETROL can be administered at any time of the day, with or without food.

Use in Renal Impairment

Monotherapy

In patients with renal impairment, no dosage adjustment of EZETROL is necessary (see Characteristics in Patients [Special Populations]).

Combination Therapy with Simvastatin

In patients with renal insufficiency, no dosage adjustment of EZETROL is necessary. In patients with mild to moderate renal insufficiency, no dosage adjustment of simvastatin is necessary. In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosages of simvastatin above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously. *(*see PRECAUTIONS, Characteristics in Patients [Special Populations] and labeling of simvastatin.)

Use in the Elderly

No dosage adjustment is required for elderly patients (see *Characteristics in Patients [Special Populations]*).

Use in Pediatric Patients

Children and adolescents ☐ 10 years: No dosage adjustment is required (see *Characteristics in Patients [Special Populations]*).

Children < 10 years: Treatment with EZETROL is not recommended.

Use in Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6). Treatment with ezetimibe is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction. (see PRECAUTIONS and *Characteristics in Patients [Special Populations].*)

Co-administration with bile acid sequestrants

Dosing of EZETROL should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

When EZETROL is to be administered with a statin or with fenofibrate, please refer to the Package Insert for that particular medication.

PRECAUTIONS

When EZETROL is to be administered with a statin or with fenofibrate, please refer to the Package Insert for that particular medication.

Liver Enzymes

In controlled co-administration trials in patients receiving EZETROL with a statin, consecutive transaminase elevations (☐3 X the upper limit of normal [ULN]) have been observed. When EZETROL is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin. (see SIDE EFFECTS.)

In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomized to receive EZETROL 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (≥3 X ULN) was 0.7% for EZETROL combined with simvastatin and 0.6% for placebo. (see SIDE EFFECTS.)

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with EZETROL compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for EZETROL vs 0.1% for placebo, and 0.1% for EZETROL co-administered with a statin vs 0.4% for statins alone.

In post-marketing experience with EZETROL, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating EZETROL. However, rhabdomyolysis has been reported very rarely with EZETROL monotherapy and very rarely with the addition of EZETROL to agents known to be associated with increased risk of rhabdomyolysis. All patients starting therapy with EZETROL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. EZETROL and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy.

In a clinical trial in which over 9000 patients with chronic kidney disease were randomized to receive EZETROL 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for EZETROL combined with simvastatin and 0.1% for placebo. (see SIDE EFFECTS.)

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, EZETROL is not recommended in these patients (see *Characteristics in Patients [Special Populations]*).

Fibrates

The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of EZETROL and fibrates (other than fenofibrate) is not recommended (see DRUG INTERACTIONS).

Fenofibrate

If cholelithiasis is suspected in a patient receiving EZETROL and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see SIDE EFFECTS and the Package Insert for fenofibrate).

Cyclosporine

Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving EZETROL and cyclosporine (see DRUG INTERACTIONS).

Anticoagulants

If EZETROL is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (See DRUG INTERACTIONS).

PREGNANCY

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple dose studies of ezetimibe given in combination with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When EZETROL is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor.

Labor and Delivery

The effects of EZETROL on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, EZETROL should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

DRUG INTERACTIONS

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

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of 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 AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction.

Cyclosporine: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, 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 from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. 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 cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see PRECAUTIONS).

Fibrates: The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see SIDE EFFECTS and CLINICAL STUDIES, *Co-administration with Fenofibrate*); co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of EZETROL with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

Statins: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

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. There have been post-marketing reports of increased International Normalized Ratio in patients who had EZETROL added to warfarin or fluindione. Most of these patients were also on other medications (See PRECAUTIONS).

SIDE EFFECTS

Clinical studies of up to 112 weeks duration in which EZETROL 10 mg daily was administered alone (n=2396) with a statin (n=11,308), or with fenofibrate (n=185), patients demonstrated: EZETROL was generally well tolerated, adverse reactions were usually mild and transient, the overall incidence of side effects reported with EZETROL was similar to that reported with placebo, and the discontinuation rate due to adverse experiences was comparable between EZETROL and placebo.

The following common (≥1/100, <1/10) or uncommon (≥1/1000, <1/100), drug-related adverse experiences were reported in patients taking EZETROL alone (n=2396) and at a greater incidence than placebo (n=1159), or in patients taking Ezetrol co-administered with a statin (n =11,308) and at a greater incidence than statin administered alone (n=9361).

EZETROL administered alone:

Investigations:

Uncommon: ALT and/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: cough

Gastrointestinal Disorders:

Common: abdominal pain; diarrhea; flatulence

Uncommon: dyspepsia; gastroesophageal reflux disease; nausea

Musculoskeletal and Connective Tissue Disorders

Uncommon: arthralgia; muscle spasms; neck pain

Metabolism and Nutrition Disorders:

Uncommon: decreased appetite

Vascular Disorders:

Uncommon: hot flush; hypertension

General Disorders and Administration Site Condition:

Common: fatigue

Uncommon: chest pain; pain

EZETROL co-administered with a statin:

Investigations:

Common: ALT and/or AST increased

Nervous System Disorders:

Common: headache

Uncommon: paresthesia

Gastrointestinal Disorders

Uncommon: dry mouth; gastritis

Skin and Subcutaneous Tissue Disorders

Uncommon: pruritus; rash; urticaria

Musculoskeletal and Connective Tissue Disorders

Common: myalgia

Uncommon: back pain; muscular weakness; pain in extremity

General Disorders and Administration Site Condition

Uncommon: asthenia; edema peripheral

EZETROL co-administered with fenofibrate:

Gastrointestinal Disorders

Common: abdominal pain

In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to 1 year. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy and EZETROL co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (0.0, 3.1) and 1.7% (0.6, 4.0) for fenofibrate monotherapy and EZETROL co-administered with fenofibrate, respectively (see PRECAUTIONS). There were no CPK elevations > 10 X ULN in either treatment group in this study.

Patients with Chronic Kidney Disease

In the Study of Heart and Renal Protection (SHARP), involving over 9000 patients treated with a fixed dose combination of EZETROL 10 mg with simvastatin 20 mg daily (n=4650) or placebo (n=4620), the median follow-up period is 4.9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4% in patients treated with EZETROL combined with simvastatin, 9.8% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2% in patients treated with EZETROL combined with simvastatin and 0.1% in patients treated with placebo. Consecutive elevations of transaminases (> 3X ULN) occurred in 0.7% of patients treated with EZETROL combined with simvastatin compared with 0.6% of patients treated with placebo. In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for EZETROL combined with simvastatin, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

Laboratory Values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between EZETROL (0.5 %) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with EZETROL co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. (See PRECAUTIONS.)

Clinically important elevations of CPK (≥10 X ULN) in patients treated with EZETROL administered alone or co-administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

Post-marketing Experience

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

Blood and lymphatic system disorders: thrombocytopaenia

Nervous system disorders: dizziness; paraesthesia

Gastrointestinal disorders: pancreatitis; constipation

Skin and subcutaneous tissue disorders: erythema multiforme

Musculoskeletal and connective tissue disorders: myalgia; myopathy/rhabdomyolysis (See V. PRECAUTIONS)

General disorders and administration site conditions: asthenia

Immune system disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria

Hepatobiliary disorders: hepatitis; cholelithiasis; cholecystitis

Psychiatric disorders: depression

OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks, was generally well tolerated.

A few cases of overdosage with EZETROL have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

STORAGE

Store at or below 30°C (86°F). Protect from moisture.

AVAILABILITY

Manufactured by MSD International GmbH (Puerto Rico Branch) LLC. Pridco Industrial Park, State Road #183, Las Piedras, Puerto Rico 00771.