Fig. 4 添付文書中に記載されているCYP分子種 (薬効群別調査)

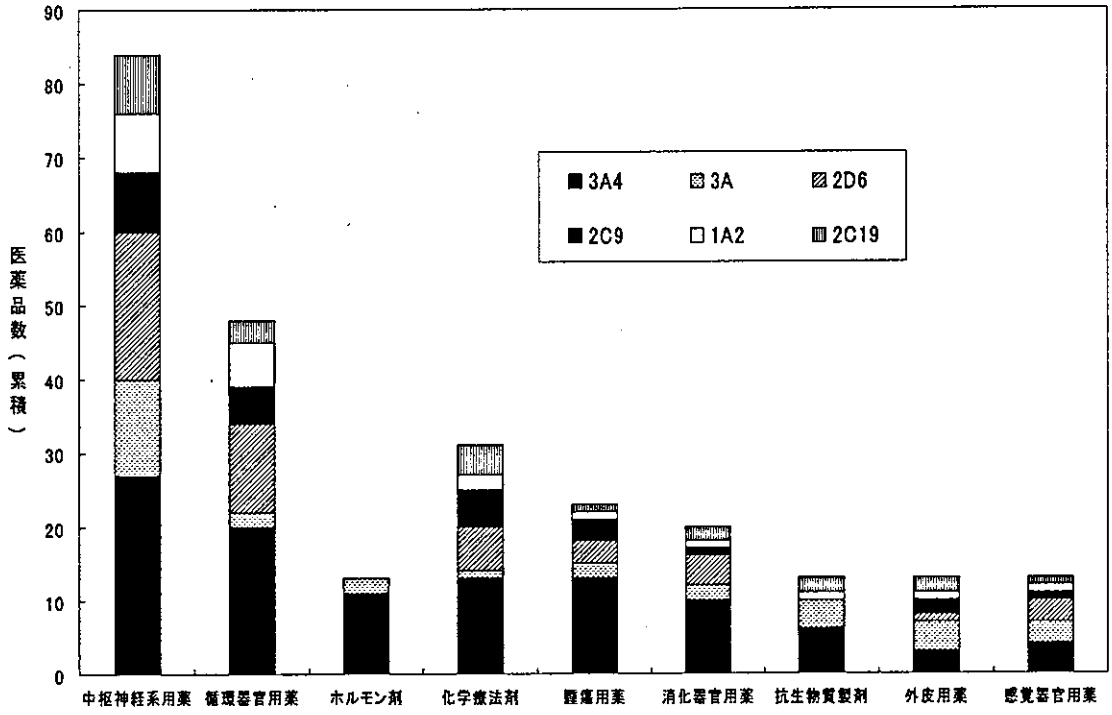
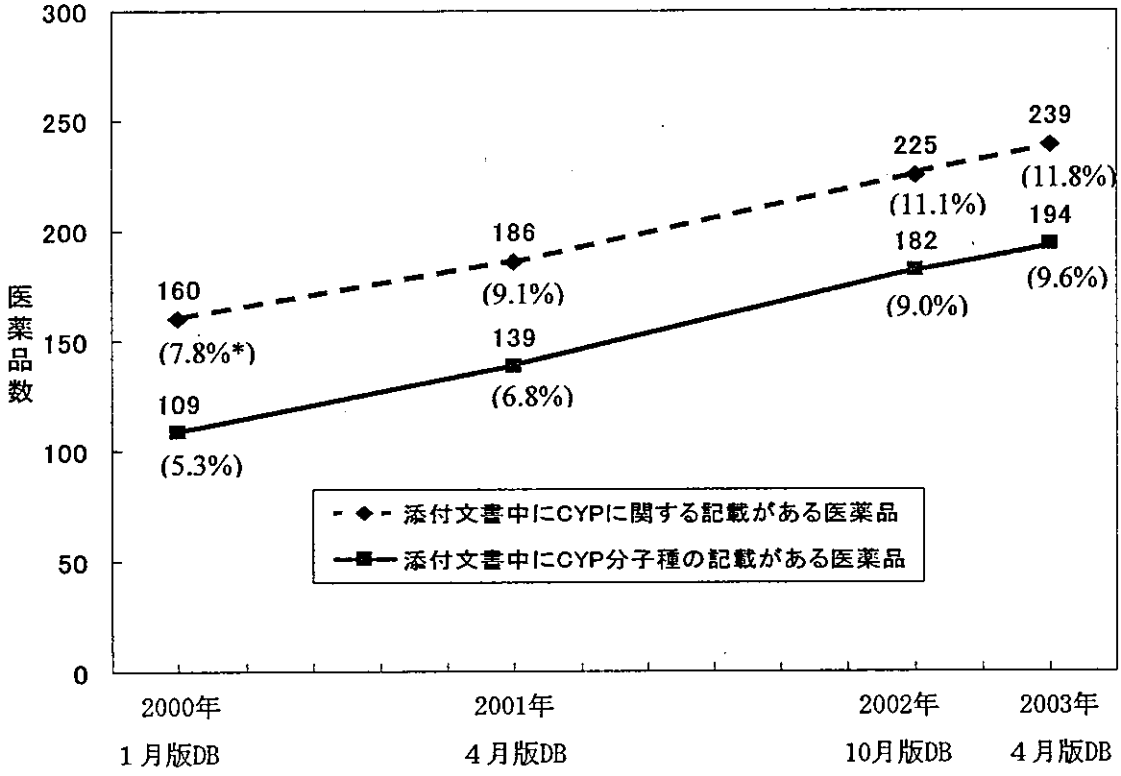


Fig. 5 添付文書中にCYPに関連する記載がある医薬品数の年代別推移



*(添付文書中にP450に関する記載がある医薬品数/薬効群中の全医薬品数)

Fig 6　添付文書中に主なCYP分子種の記載がある医薬品数の年次別推移

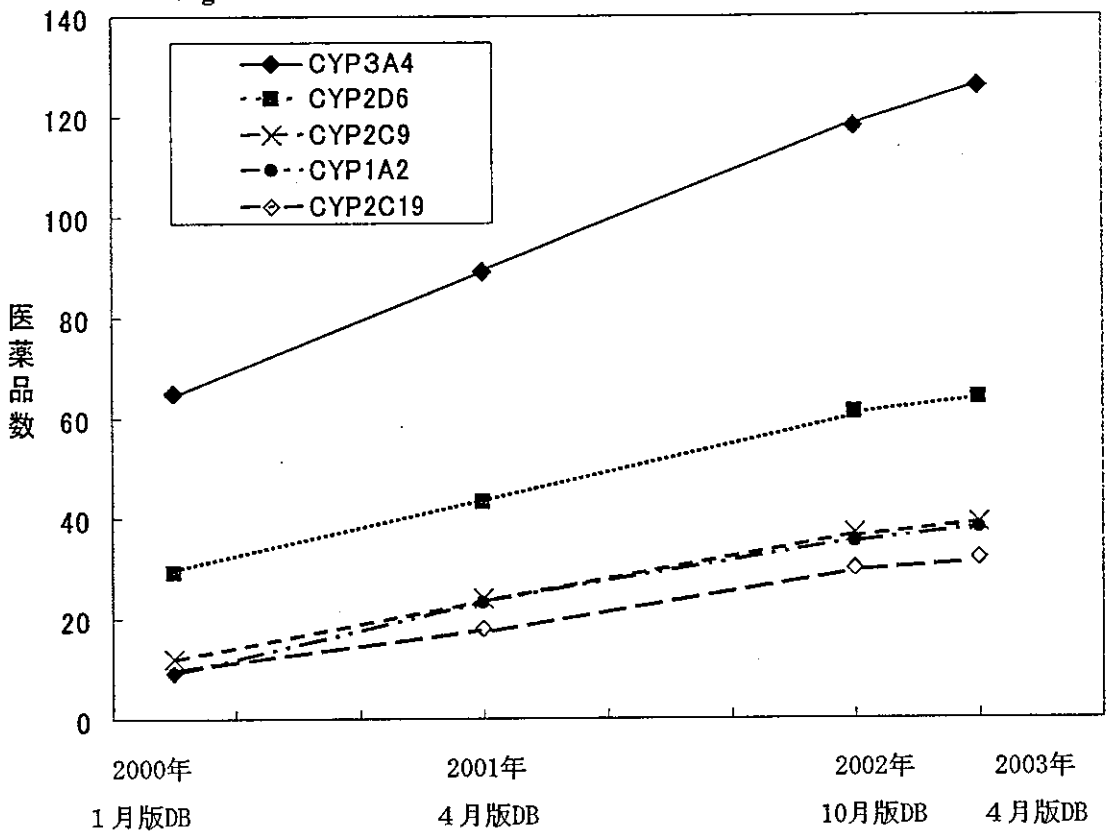


Fig. 7　医薬品の承認取得年と添付文書中のCYPに関する記載との関連性

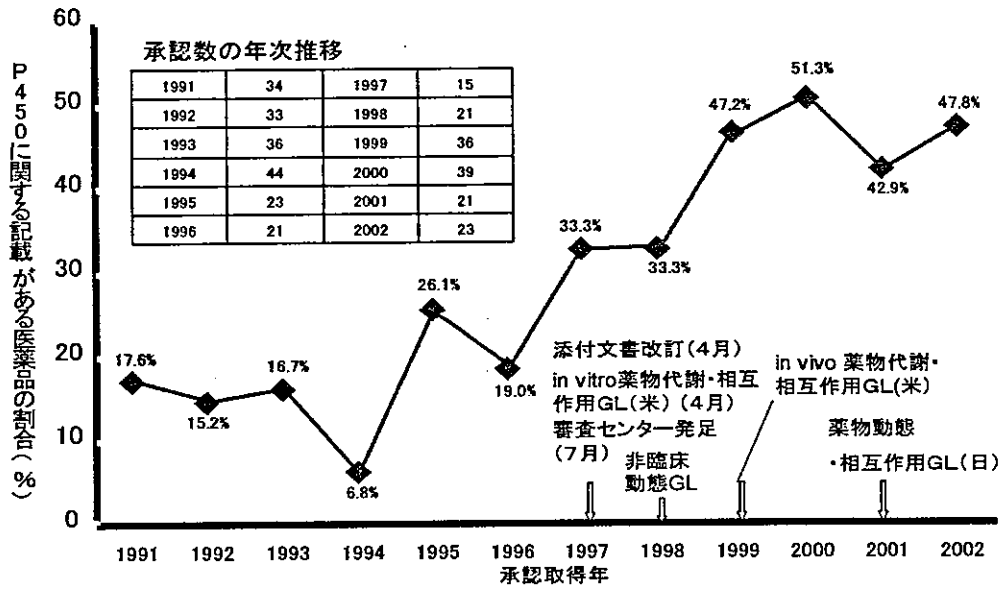
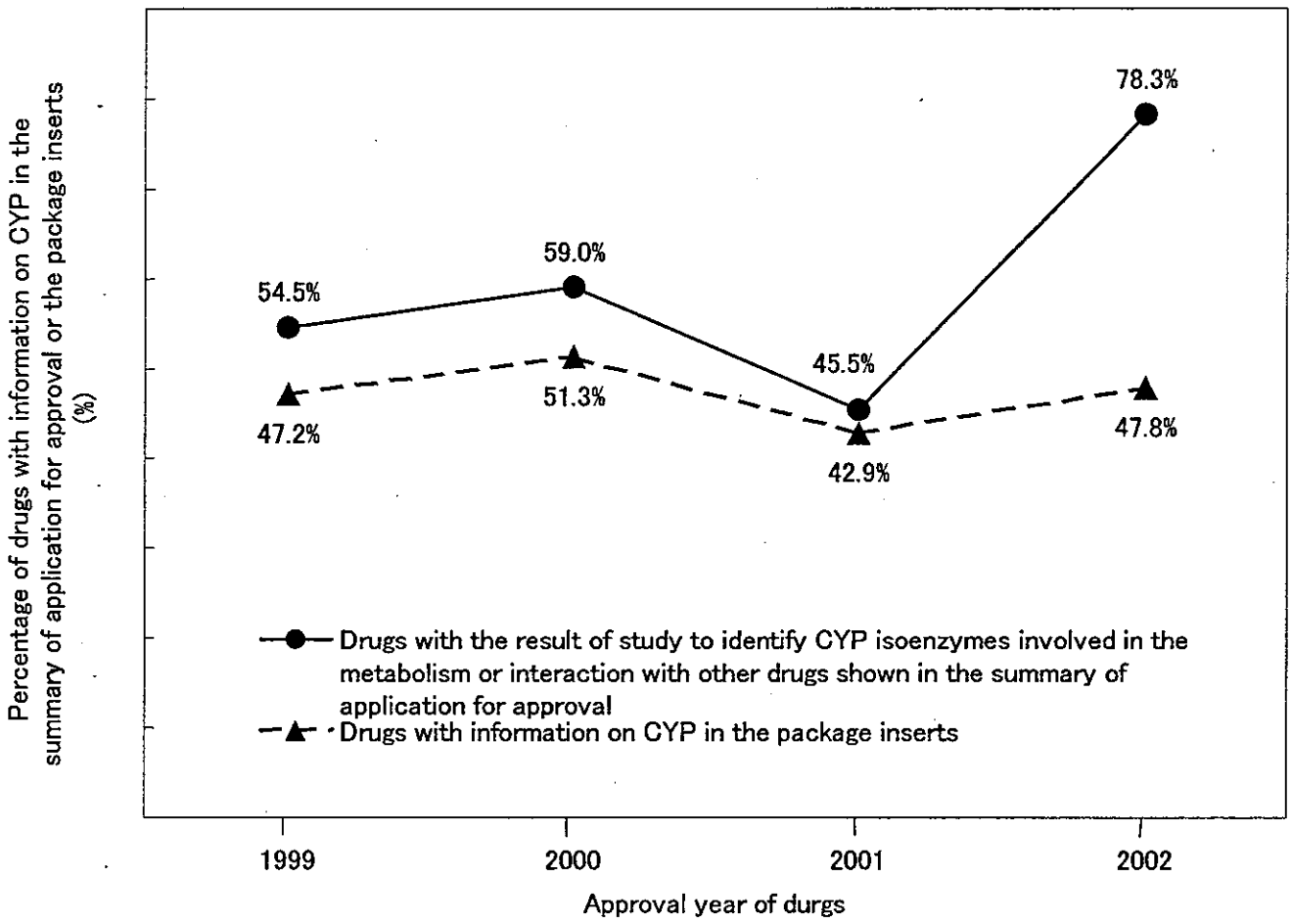


Fig. 8　承認申請時におけるCYP分子種の特定を目的とした試験の実施状況



For drugs with new active ingredients approved from September 1999 to 2002, the summaries of application for approval were searched for studies to identify CYP isoenzymes involving in the metabolism and interaction with other drugs. The number of drugs, on which the study was conducted at application for approval, was counted by the approval year, and the percentage to all drugs approved each year was calculated.

Table 3: The extent of increase in AUC and Cmax of drugs in group 1 by combination with grapefruit juice

	Oral bioavailability	AUC	Cmax	References
Terfenadine	<2%	2.5	3.4	Clifford and others 1997
Saquinavir	1-4%	2.2	2.2	Fuhr 1998
Buspirone	4-5%	9.2	4.2	Lilja and others 1998a
Simvastatin	<5%	16.1	9.4	Lilja and others 1998b
Lovastatin	5%	15.3	11.8	Kantola and others 1998
17β-estradiol	5%	1.2*	1.3*	Schubert and others 1994
Nisoldipine	5-8%	4.1	4.9	Takanaga and others 2000a
Nimodipine	5-10%	1.5	1.2	Fuhr and others 1998
Progesterone	9%	1.3	n.d.	Fingerova and others 2003
Dextromethorphan	10% [rat]	5.4 [bioavailability]		Di Marco and others 2002
Atrovastatin	12%	2.5	1.1	Lilja and others 1999
Felodipine	14%	3.3	2.9	Edgar and others 1992
Propafenone	15-25%	1.3	1.2	Bailey and others 1998a
Nitrendipine	5-30%	2.3	2.1	Soons and others 1991
Midazolam	25-40%	5.9	2.7	Veronese et al., 2003
Scopolamine	3-50%	1.4	0.94	Ebert and others 2000
Cyclosporine	30% [highly variable]	1.6	1.4	Ducharme and others 1995
Nicardipine	15-45%	2.0	n.d.	Uno and others 2000
Erythromycin	32%	1.5	1.5	Kanazawa and others 2001
Verapamil	30-40%	1.4	1.6	Fuhr and others 2002
Sildenafil	40%	1.2	1.0	Jetter and others 2002
Cisapride	40-50%	2.6	1.8	Desta and others 2001
Diltiazem	40-50%	1.2	1.1	Christensen and others 2002
Ethinylestradiol	40-50%	1.3**	1.4**	Weber and others 1996
Nifedipine	50-60%	2.0	1.9	Sigusch and others 1994
Triazolam	60%	2.4	1.4	Lilja and others 2000b
Prednisone	62%	1.5	1.4	Hollander and others 1995

Amiodarone	67%	1.5	1.8	Libersa and others 2000
Digoxin	65-75%	1.1	1.2	Becquemont and others 2001
Carbamazepine	70-85%	1.4	1.4	Garg and others 1998
Diazepam	75%	3.2	1.5	Ozdemir and others 1998
Praziquantel	>80%	1.9	1.62	Castro and others 2002
Amlodipine	81%	1.2	1.2	Josefsson and others 1996
Methylprednisolone	82-92%	1.8	1.3	Varis and others 2000
Caffeine	100%	1.3	n.d.	Fuhr and others 1993
Halofantrine	n.d. [highly variable]	2.8	3.2	Charbit and others 2002
Artemether	n.d. [low]	3.5	2.6	van Agtmael and others 1999
Sertraline	n.d.	1.47 [trough serum concentrations]		Lee and others 1999

Data with the maximum change in AUC is adopted in this Table. The change in AUC and Cmax are shown as the ratio to the value in control. If the change in either AUC or Cmax was more than 1.2 fold, the drug is assigned in group 1. Statistical information given, significant grapefruit juice effect ($p < 0.05$) is indicated by boldface.

Drugs with underline are newly reported drugs on the interaction with grapefruit juice since two reviews were published at 1998.

n.d.: no available data

*: Bevarage not containing flavonoids (probably not contain furanocoumarins, too) was given as control.

**: Herbal tea was given as control.

Table 4: Drugs in group 2, the primaly metabolic enzyme and the oral bioavailability

	Primaly metabolic enzyme	Oral bioavailability	References
Pravastatin	Hydroxylase	20%	Lilja and others 1999
Amitriptyline	CYP2D9, CYP2C19, CYP1A2	33-62%	Vandel and others 1999
Acenoucoumarol	CYP2C9	>80%	van Rooij and others 1993
Phenytoin	CYP2C9	n.d.	Kumar and others 1999
Desloratadine	Not identified (unlikely CYP3A4 and CYP2C6)	n.d.	Banfield and others 2002
Clozapine	CYP1A2, CYP3A4	27-50 %	Vandel and others 2000 Lane and others 2001
Losartan	CYP2C9, CYP3A4	33%	Zaidenstein and others 2001
Omeprazole	CYP2C19, CYP3A4	54%	Tassaneeyakul and others 2000
Clomipramine	CYP1A2, CYP3A4	<62%	Vandel and others 1999
Clarithromycin	CYP3A4	55%	Cheng and others 1998
Indinavir	CYP3A4	65%	Penzak and others 2002 Shelton and others 2001
Quinidine	CYP3A4	70%	Min and others 1996
Quinine*	CYP3A4	88%	Ho and others 1999
Alprazolam	CYP3A4	80-100%	Yasui and others 2000

Drugs with underline are newly reported drugs on the interaction with grapefruit juice since two reviews were published at 1998. n.d.: no available data

*: Orange juice (common) was given as control. Although decrease by more than 20% in the AUC was observed in combination with 50 % grapefruit juice, it is considered in range of the dispersion because of the decrease only by 5% with 100% grapefruit juice.

Table 5: The extent of decrease in AUC and Cmax of drugs in group 3 by combination with grapefruit juice

		Parent Drug		
	Oral bioavailability	AUC	Cmax	References
Itraconazole	30-40%	0.57	0.64	Penzak and others 1999
Fexofenadine	33%	0.33	0.38	Dresser and others 2002
Amprenavir	n.d.	0.90	0.78	Demarles and others 2002
Etoposide	47-76%	0.76	n.d.	Reif and others 2002
Celiprolol	30-70%	0.15	0.05	Lilja and others 2003
Theophylline	100%	0.75	0.82	Gupta and others 1999

Data with the maximum change in AUC is adopted in this Table. The change in AUC and Cmax are shown as the ratio to the value in control. If the change in either AUC or Cmax was less than 0.8 fold, the drug is assigned in group 3. Statistical information given, significant grapefruit juice effect ($p < 0.05$) is indicated by boldface.
Drugs with underline are newly reported drugs on the interaction with grapefruit juice since two reviews were published at 1998.
n.d.: no available data

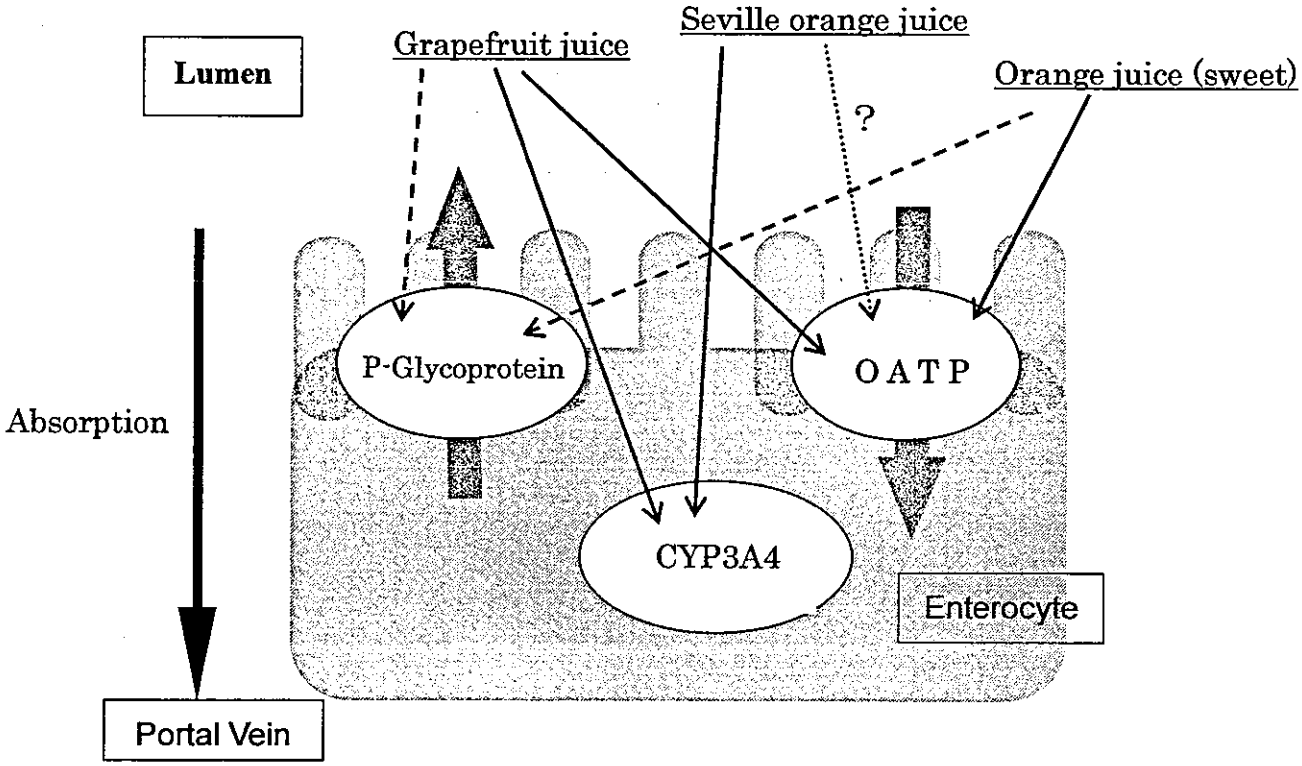
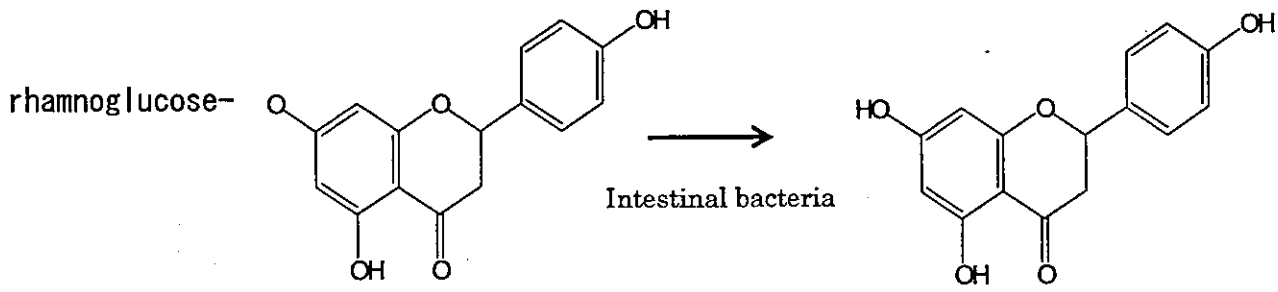
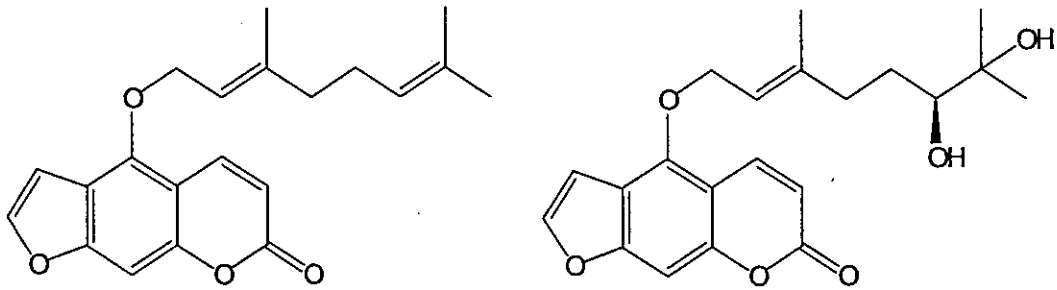


Fig.9. The target sites in enterocytes of small bowel by various citrus juices



Naringin Naringenin

Fig.10: Chemical structures of naringin and naringenin



Bergamottin 6',7'-Dihydroxybergamottin

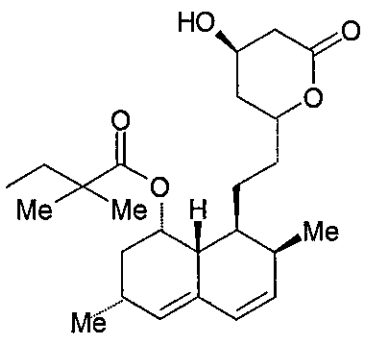
Fig.11: Chemical structures of bergamottin and 6',7'-dihydroxybergamottin

Table 6. Dosage and year of approval of statins.

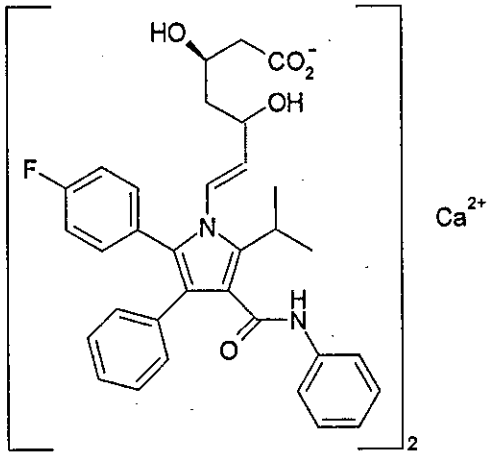
	Japan		USA	
	Dose (mg/day)	Approval year	Dose (mg/day)	Approval year
Simvastatin	5-20 [a]	1991	5-80	1991
Atorvastatin	10-40	2000	10-80	1996
Fluvastatin	20-60	1998	40-80 [b]	1993
Pravastatin	10-20	1991	40-80	1991
Pitavastatin	1-4	2003	Not approved	Not approved

a 5-10 mg/day in original. Increased to 20 mg/day after amendment in 2001.

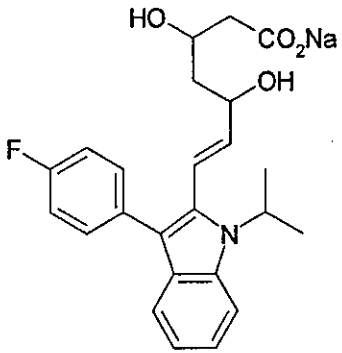
b Recommended starting dose is 20-40 mg/day.



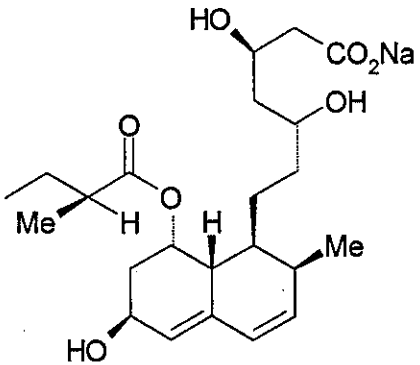
Simvastatin



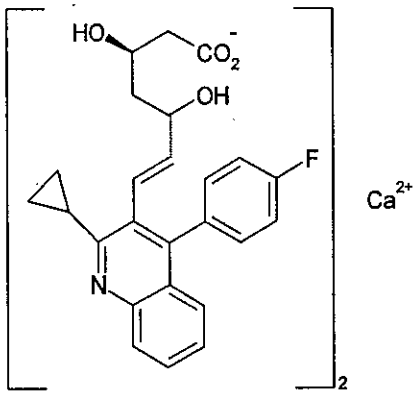
Atorvastatin



Fluvastatin



Pravastatin



Pitavastatin

Fig. 12 Chemical Structures of Statins.

Table 7. Enzymes involved in the metabolism of statins and the description in the package inserts.

	Responsible enzyme	Package insert (Japan)		Package insert (USA)	
		Drug interaction	Pharmacokinetics	Drug interaction	Pharmacokinetics/Metabolism
Simvastatin	CYP3A4 [1]	CYP3A4	–	CYP3A4 (also in warning section)	CYP3A4
Atorvastatin	CYP3A4 [1]	CYP3A4	CYP3A4	cytochrome P450 3A4	Cytochrome P450 3A4
Fluvastatin	Mainly CYP2C9 [1),2)]	–	CYP2C9	2C9 (75 %), 2C8 (5%), 3A4 (20%)	2C9 (75 %), 2C8 (5%), 3A4 (20%)
Pravastatin	Not metabolized significantly by CYPs [1]	–	Not metabolized by CYP 3A4	Not metabolized by cytochrome P450 3A4	–
Pitavastatin	Metabolized slightly by CYP2C9 [3),4)]	Hardly metabolized (slightly metabolized by CYP2C9)	Slightly metabolized (CYP2C9)	Not approved	Not approved

1) Williams D, Feely J. (2002) Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clinical Pharmacokinetics, 41, 343-370
2) Scripture CD, Pieper JA. (2001) Clinical pharmacokinetics of fluvastatin. Clinical Pharmacokinetics, 40, 263-281
3) Fujino H, Yamada I, Shimada S, Nagao T, Yoneda M. (2002) Metabolic fate of pitavastatin (NK-104), a new inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase. Effects on drug-metabolizing systems in rats and humans. Arzneimittel-Forschung, 52, 745-753.
4) Kajinami K, Takekoshi N, Saito Y. (2003) Pitavastatin: efficacy and safety profiles of a novel synthetic HMG-CoA reductase inhibitor. Cardiovascular Drug Reviews, 21, 199-215

Table 8. Pharmacokinetic information on simvastatin drug interactions and the description in the package insert.

	Literature: Changes of AUC	Japan			US		
		Status	Mechanism	Quantitative data / dose adjustment	Section of statement	Mechanism	Quantitative data / dose adjustment
Itraconazole	10–19 fold [1)2)]	Contra-indication	inhibition of CYP 3A4	—	Warning	potent inhibitor of CYP 3A4	—
Miconazole	No report						
Erythromycin	6.2 fold [3)]	Precaution	possible CYP3A4 inhibition	—			
Clarithromycin	No report	Precaution	possible CYP3A4 inhibition	—			
Ritonavir + Saquinavir [a)]	31 fold [4)5)]	Precaution	possible CYP3A4 inhibition	—			
Nelfinavir	6 fold [6)]						
Cyclosporine	3–8 fold [7)–9)]	Precaution	possible CYP3A4 inhibition	not exceed 10 mg/day			Should not exceed 10 mg/day
Gemfibrozil [b)]	2 fold [10)]	—				—	Should not exceed 10 mg/day
Rifampicin	0.10 fold [11)]	—			—		
Verapamil	4.6 fold [3)]	—			Warning	—	Should not exceed 20 mg/day
Diltiazem	5 fold [12)]	—			—		
Troglitazone [c)]	0.6 fold [13)]	—			—		
Pioglitazone	No change [13)]	—			—		
Irbesartan	No change (acid form) [14)]	—			—		
Digoxin	1.20 fold (AUC of digoxin) [15)]	—			Drug interactions	—	Slight elevation of digoxin in plasma (less than 0.3 ng/mL)
Grapefruit juice	3.6–16 fold [16)–18)]	Other precautions	—	A report of clinical study [d)]	Warning	Potent inhibitor of CYP 3A4	Less than 1 quart (0.95L) of grape fruit juice, Study 1: 16 folds Study 2: 1.88 fold

—: No data.
a Ritonavir plus saquinavir soft-gel capsules
b Not approved in Japan
c Withdrawn from Japan and US in 2000
d It has been reported that a large amount (>1.14 L daily) of grapefruit juice increases blood simvastatin level

1) Williams D, Feely J. (2002) Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clinical Pharmacokinetics, 41, 343-370.
2) Neuvonen PJ, Kantola T, Kivisto KT. (1998) Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor

itraconazole. Clinical Pharmacology and Therapeutics, 63, 332-341
3) Kantola T, Kivisto KT, Neuvonen PJ. (1998) Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. Clinical Pharmacology and Therapeutics, 64, 177-182.
4) Fichtenbaum CJ, Gerber JG. (2002) Interactions between anti-retroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. Clinical Pharmacokinetics, 41, 1195-1211
5) Fichtenbaum CJ, Gerber JG, Rosenkranz SL, Segal Y, Aberg JA, Blaschke T, Alston B, Fang F, Kosel B, Aweeka F. (2002) Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS (London, England), 16, 569-577
6) Hsyu PH, Schultz-Smith MD, Lillibridge JH, Lewis RH, Kerr BM. (2001) Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. Antimicrobial Agents and Chemotherapy, 45, 3445-3450
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9) Ichimaru N, Takahara S, Kokado Y, Wang JD, Hatori M, Kameoka H, Inoue T, Okuyama A. (2001) Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. Atherosclerosis, 158, 417-423
10) Backman JT, Kyrklund C, Kivisto KT, Wang JS, Neuvonen PJ. (2000) Plasma concentrations of active simvastatin acid are increased by gemfibrozil. Clinical Pharmacology and Therapeutics, 68, 122-129
11) Kyrklund C, Backman JT, Kivisto KT, Neuvonen M, Laitila J, Neuvonen PJ. (2000) Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. Clinical Pharmacology and Therapeutics, 68, 592-597.
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13) Prueksaritanont T, Vega JM, Zhao J, Gagliano K, Kuznetsova O, Musser B, Amin RD, Liu L, Roadcap BA, Dilzer S, Lasseter KC, Rogers JD. (2001) Interactions between simvastatin and troglitazone or pioglitazone in healthy subjects. Journal of Clinical Pharmacology, 41, 573-581.
14) Marino MR, Vachharajani NN, Hadjilambris OW. (2000) Irbesartan does not affect the pharmacokinetics of simvastatin in healthy subjects. Journal of Clinical Pharmacology, 40, 875-879.
15) Todd PA, Goa KL. (1990) Simvastatin. A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. Drugs, 40, 583-607
16) Lilja JJ, Neuvonen M, Neuvonen PJ. (2004) Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. British Journal of Clinical Pharmacology, 58, 56-60
17) Lilja JJ, Kivisto KT, Neuvonen PJ. (2000) Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. Clinical Pharmacology and Therapeutics, 68, 384-390
18) Lilja JJ, Kivisto KT, Neuvonen PJ. (1998) Grapefruit juice-simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. Clinical Pharmacology and Therapeutics, 64, 477-483.

Table 9. Pharmacokinetic information on atorvastatin drug interactions and the description in the package insert.

	Literature: Changes of AUC	Japan			US		
		Status	Mechanism	Quantitative data / dose adjustment	Section of statement	Mechanism	Quantitative data / dose adjustment
Itraconazole	2.5–4 fold [1)2)]	Precaution	Inhibition of metabolism	—	Warning	—[d)]	—
Erythromycin	1.33 fold (Cmax:1.38 folds) [3)]	Precaution	Inhibition of metabolism	—	Warning	Inhibition of CYP3A4	40% increase(as plasma concentration)
Azithromycin	No change [4)]	—			—		
Clarithromycin	1.8 fold [4)]	Precaution	Inhibition of metabolism	Increase 81.8 %	—		
Ritonavir + Saquinavir [a)]	3.5 fold [5)]	Precaution	Inhibition of CYP 3A4	1.7 fold (Nelfinavir)	—		
Nelfinavir	1.7 fold [6)]						
Cyclosporine	6 fold (activity [c)]) [7)]	Precaution	Inhibition of metabolism and bile exclusion	—	Warning	—[d)]	—
Cimetidine	No change [8)]	—			Drug interactions	—	Not altered (plasma concentration)
Troglitazone [b)]	0.67 fold [9)]	—			—		
Digoxin	1.15 fold for digoxin [10)]	Precaution	Inhibition of digoxin exclusion via P-glycoprotein	3.6–14.8% (digoxin AUC)	Drug interactions	—	20 % increase (steady-state plasma digoxin concentration)
Grapefruit juice	1.4–2.5 fold [11)12)]	—			—		

–: No data.
a Ritonavir plus saquinavir soft-gel capsules.
b Withdrawn from the market in Japan and USA.
c HMG-CoA reductase inhibitory activity (parent drug and metabolites).
d Risk of rhabdomyolysis.

1) Mazzu AL, Lasseter KC, Shamblen EC, Agarwal V, Lettieri J, Sundaresen P. (2000) Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. Clinical Pharmacology and Therapeutics, 68, 391-400.
2) Kantola T, Kivisto KT, Neuvonen PJ. (1998) Effect of itraconazole on the pharmacokinetics of atorvastatin. Clinical Pharmacology and Therapeutics, 64, 58-65.
3) Siedlik PH, Olson SC, Yang BB, Stern RH. (1999) Erythromycin coadministration increases plasma atorvastatin concentrations. Journal of Clinical Pharmacology, 39, 501-504
4) Amsden GW, Kuye O, Wei GC. (2002) A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. Journal of Clinical Pharmacology, 42, 444-449.
5) Fichtenbaum CJ, Gerber JG. (2002) Interactions between anti-retroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. Clinical Pharmacokinetics, 41, 1195-1211
6) Hsyu PH, Schultz-Smith MD, Lillibridge JH, Lewis RH, Kerr BM. (2001) Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. Antimicrobial Agents and Chemotherapy, 45, 3445-3450
7) Asberg A, Hartmann A, Fjeldsa E, Bergan S, Holdaas H. (2001) Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 1, 382-386.
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9) Loi CM, Sedman AJ. (1999) Response to Lin and Ito. Effect of troglitazone on atorvastatin pharmacokinetics and pharmacodynamics. Diabetes Care, 22, 2105-2106.
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inhibition of I ntestinal P-glycoprotein-mediated secretion. Journal of Clinical Pharmacology, 40, 91-98
11) Fukazawa I, Uchida N, Uchida E, Yasuhara H. (2004) Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. British Journal of Clinical Pharmacology, 57, 448-455
12) Lilja JJ, Kivisto KT, Neuvonen PJ. (1999) Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. Clinical Pharmacology and Therapeutics, 66, 118-127

Table 10. Pharmacokinetic information on fluvastatin drug interactions and the description in the package insert.

	Literature: Changes of AUC	Japan			US		
		status	mechanism	quantitative data / dose adjustment	section of statement	mechanism	quantitative data / dose adjustment
Itraconazole	No change [1]	—			Drug interactions	CYP 3A4 inhibitor/substrate	does not affect plasma levels
Fluconazole	1.84 fold [2]				—		
Ketoconazole [a]	No change [3]						
Erythromycin	No change [3]	Precaution	—		Warning	CYP 3A4 inhibitor/substrate	did not affect steady-state plasma levels
Cyclosporine	3–3.3 fold [4][5]	Precaution	—		Warning	CYP 3A4 inhibitor/substrate	AUC: 1.9 fold, Cmax: 1.3 fold
Bezafibrate	No report	Precaution	possible high plasma level via inhibition of liver metabolism	—	Warning	—[c]	—
Gemfibrozil [b]	No change [5]	—			Warning	—	no change in plasma levels
Rifampicin	0.5 fold [3]	Precaution	induction of liver metabolic enzyme	—	Drug interactions	—	0.49 fold
Cimetidine	1.24–1.33 fold [3]	Precaution	possible high plasma level via inhibition of liver metabolism	—	Drug interactions	—	1.24–1.33 fold
Ranitidine		Precaution	possible high plasma level via inhibition of liver metabolism	—			
Omeprazole		Precaution	possible high plasma level via inhibition of liver metabolism	—			
Propranolol	No change [7]	—			Drug interactions	—	no change for bioavailability
Diclofenac	1.1–1.54 fold for fluvastatin, 1.1–1.3 fold for diclofenac [3][6]	—			Drug interactions	—	1.3 fold for diclofenac AUC
Tolbutamide	No change [9]	—			Drug interactions	—	did not affect
Glibenclamide	No change [9]	—			Drug interactions	—	1.5 fold
Warfarin	No change for warfarin level [7]	Precaution	not cleared	—	Drug interactions		no elevation of warfarin concentration
Digoxin	No change of digoxin AUC [10][11], Cmax of digoxin: 1.2 fold [12]	Precaution	not cleared	—	Drug interactions	—	AUC: No change, Cmax: 1.11 fold (for digoxin)

—: No data
a Only topical form is approved in Japan.
b Not approved in Japan.

c Fibrates alone associated with myopathy.

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Table 11. Pharmacokinetic information on pravastatin drug interactions and the description in the package insert.

	Literature: Changes of AUC	Japan			US		
		Status	Mechanism	Quantitative data / dose adjustment	Section of statement	Mechanism	Quantitative data / dose adjustment
Itraconazole	slightly increase – 1.5 fold [1)2)]		No effect on pravastatin metabolism		Drug interactions	Inhibition of p-glycoprotein (also known as CYP 3A4 inhibitor)	AUC: 1.7 fold, Cmax: 2.5 fold
Fluconazole	No change [3)]	—			—		
Ritonavir + Saquinavir [a)]	0.5 fold [4)]	—			—		
Cyclosporine	5–12 fold [5)6)]	Precaution	—	—	Warning	—	Pravastatin level: increase (one study),cyclosporine level: no elevations, should begin 10mg/day,maximum 20mg/day
Fenofibrate	No change [7)]	Precaution	(synergistic adverse effect)	—	Warning	—[d)]	—
Gemfibrozil [b)]	2 fold [8)]	—			Warning	—	Significant increase (metabolite)
Rifampicin	0.69 fold [9)]	—			—		
Diltiazem	No effects [10)]		no effect on pravastatin metabolism		Drug interactions	Weak CYP 3A4 inhibitor	No change
Mibefradil [c)]	No change [11)]	—			Drug interactions	CYP 3A4 inhibitor	—
Propranolol	0.77 fold [12)]	—			—		
Digoxin	Increase for pravastatin, no change on digoxin [13)]	—			Drug interactions	—	Digoxin bioavailability: not affected, AUC of pravastatin: tended to increase
Grapefruit juice	No change [14)15)]	—			—		

–: No data.
a Ritonavir plus saquinavir soft-gel capsules.
b Not approved in Japan.
c Not approved in Japan and withdrawn from the market in USA.
d Risk of rhabdomyolysis.

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Table 12. Pharmacokinetic information on pitavastatin drug interactions and the description in the package insert.

	Literature: Changes of AUC	Japan		
		Status	Mechanism	Quantitative data / dose adjustment
Cyclosporine	4.55 fold [1]	Contraindication	—	AUC: 4.6 fold, Cmax: 6.6 fold,
Fenofibrate	1.18 fold [2]	Contraindication (as fibrates)	Either drugs are known to induce rhabdomyolysis	1.2 fold
Gemfibrozil a)	1.44 fold [2]	—		1.4 fold
Grapefruit juice	1.16 fold [2]	—		

—: No data.
a Not approved in Japan.

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Table 13. Basic information of the Ca antagonists available in the three countries.

	JAPAN			USA			UK		
	Dose (mg/day)	Year of Approval	Responsible enzymes	Dose (mg/day)	Year of Approval	Responsible enzymes	Dose (mg/day)	Year of Approval	Responsible enzymes
Dihydropiyridines									
Amlodipine	2.5-5mg	1993	P450	5-10 mg	1992	Hepatic metabolism	5-10 mg	1995	Extensively metabolised by the liver
Felodipine	5-10 mg	1994	Intestinal P450, CYP3A4	2.5-10 mg	1991	CYP3A4	5-10 mg	2002	CYP3A4
Nicardipine	40-80 mg	1981	P450	60-120 mg	1988	Extensively metabolized by the liver	60-90 mg	1998	Extensively metabolised by the liver
Nifedipine	20- 60mg	1976	Hepatic P450	30-60 mg	1981	CYP3A4	20-90 mg	1977	CYP3A4
Nisoldipine	5-10 mg	1990	CYP3A4	20-40 mg	1995	P450	10-40 mg	1998	P450
Isradipine	--			5-20 mg	1990	CYP3A4	5-10 mg	1997	P450
Nimodipine				60 mg every 4 hours for 21 days [a]	1988	P450	60 mg every 4 hours for 21 days [a]	1989	CYP3A4 in the intestinal mucosa and the liver
Lacidipine				--			2-4 mg	1993	Hepatic metabolism
Lercanidipine							10-20mg	1996	CYP3A4
Aranidipine	5-20 mg	1996	CYP3A4				--		
Azelnidipine	8-16 mg	2003	CYP3A4						
Barnidipine	10-15 mg	1992	CYP3A4						
Benidipine	2-8mg	1991	Hepatic microsomes						
Cilnidipine	5-10mg	1995	CYP3A4, partially CYP2C19						
Efonidipine	20-40 mg	1994	P450						
Manidipine	10-20mg	1990	Hepatic CYP3A4						
Nilvadipine	4-8 mg	1989	CYP3A4						
Nitrendipine	5-10mg	1990	CYP3A4						
Others									
Verapamil	40-80 mg	1965	CYP3A4	180-480mg	1982	CYP3A4	120-480 mg	2002	--
Diltiazem	90-200 mg	1974	P450	120-540 mg	1982	P450	180-400 mg	1993	--

--: Not available
a) subarachnoid hemorrhage