PTO 1128 (REV 10/91) U.S. DEPARTMENT OF COMMERCE– PATENT & TRADEMARK OFFICE

PACE DATA ENTRY CODING SHEET

1ST EXAMINER TWEST DATE 6-2-92

2ND EXAMINER DATE

APPLICATION NUMBER	TYPE APPL	FILING DATE MONTH	DAY	YEAR	SPECIAL HANDLING	GROUP ART UNIT	CLASS	SHEETS OF DRAWING
07/883398	1	05	15	92	2	1203	546	10

TOTAL CLAIMS	INDEPENDENT CLAIMS	SMALL ENTITY?	FILING FEE	FOREIGN LICENSE	ATTORNEY DOCKET NUMBER
35	1	0	990	Y	49-168-0-DIV

CONTINUITY DATA

CONTINUITY CODE	STATUS CODE	PARENT APPPLICATION SERIAL NUMBER	PARENT PATENT NUMBER	PARENT FILING DATE MONTH	DAY	YEAR
01	2	07631092		12	19	90
12	2	07233752		08	19	88
		0				
		0				
		0				

PCT/FOREIGN APPLICATION DATA

FOREIGN PRIORITY CLAIMED	COUNTRY CODE	PCT/FOREIGN APPLICATION SERIAL NUMBER	FOREIGN FILING DATE MONTH	DAY	YEAR
Y	JPX	207224/1987	08	20	87
Y	JPX	155851/1988	01	26	88
Y	JPX	63-193606	08	03	88

DOCKET NO.: 342163US68SD

OBLON SPIVAK

ATTORNEYS AT LAW

STEPHEN G. BAXTER
(703) 413-3000
SBAXTER@OBLON.COM

JACOB A. DOUGHTY
(703) 413-3000
JDOUGHTY@OBLON.COM

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

MAIL STOP: PATENT TERM EXTENSION

RE: Application Serial No.: 07/883,398
Applicants: Yoshihiro FUJIKAWA et al
Filing Date: May 15, 1992
For: QUINOLINE TYPE MEVALONOLACTONES
Group Art Unit: 1613
Examiner: L. L. STOCKTON
Patent No.: 5,856,336
Issued: January 5, 1999

SIR:

Attached hereto for filing are the following papers:

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156 AND 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 AND 1.785 (b) WITH EXHIBITS A THRU E (ONE ORIGINAL SIGNATURE PLUS FOUR COPIES)

Credit card payment is being made online (if electronically filed), or is attached hereto (if paper filed), in the amount of **$1,120.00** to cover any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Registration No. 32,884

Jacob A. Doughty
Registration No. 46,671

Customer Number
22850
(703) 413-3000 (phone)
(703) 413-2220 (fax)
(OSMMN 02/09)

DOCKET NO: 342163US68 SD

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE PATENT OF	:
YOSHIHIRO FUJIKAWA ET AL	: GROUP ART UNIT: 1613
SERIAL NO: 07/883,398	: EXAMINER: STOCKTON, L. L.
FILED: MAY 15, 1992	: PATENT NO. 5,856,336
FOR: QUINOLINE TYPE MEVALONOLACTONES	: ISSUED: JANUARY 5, 1999

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156 AND 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 AND 1.785 (b)

MAIL STOP: PATENT TERM EXTENSION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

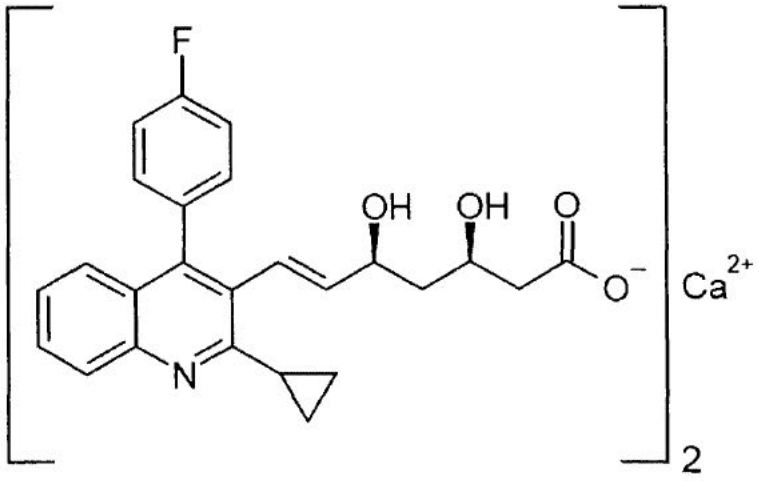
SIR:

This is an application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 and 1.785 (b) for U.S. Patent No. 5,856,336 ("the '336 patent").

Two additional copies of this application (for a total of three copies) are being submitted herewith (37 C.F.R. § 1.740(b)).

I. Complete Identification of Approved Product (37 C.F.R. § 1.740(a)(1)).

The approved product is Livalo®, which is the registered name for film-coated tablets of pitavastatin calcium. The chemical name for pitavastatin calcium is (+)monocalcium bis{(3R, 5S, 6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}. The empirical formula for pitavastatin calcium is $C_{50}H_{46}CaF_2N_2O_8$ and the molecular weight is 880.98. The structural formula is:



Each film-coated tablet of Livalo® contains 1.045 mg, 2.09 mg, or 4.18 mg of pitavastatin calcium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of the free base. The following inactive ingredients are included: lactose monohydrate, low substituted hydroxypropylcellulose, hypromellose, magnesium aluminometasilicate, magnesium stearate. The film-coating contains the following inactive ingredients: hypromellose, titanium dioxide, triethyl citrate, and colloidal anhydrous silica.

II. Complete Identification of Federal Statute under which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2)).

Regulatory permission to sell Livalo® was granted under 21 U.S.C. § 355 (section 505 of the Federal Food, Drug, and Cosmetic Act).

III. Identification of Date on which Product Received Permission for Commercial Marketing or Use (37 C.F.R. § 1.740(a)(3)).

Regulatory approval for Livalo® was granted on August 3, 2009, and a copy of the approval letter is attached hereto as Exhibit A.

IV. Identification of Each Active Ingredient in Product and Statement That Each Active Ingredient Has Not Been Previously Approved for Commercial Marketing or Use (37 C.F.R. § 1.740(a)(4)).

The sole active ingredient in the approved product is pitavastatin calcium. Pitavastatin calcium has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

V. Statement that Application Is Being Submitted within Sixty Day Period and Identification of Date of Last Day on which Application Could Be Submitted (37 C.F.R. § 1.740(a)(5)).

This application is being submitted within the sixty day period specified by 35 U.S.C. § 156(1) and 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is October 1, 2009.

VI. Complete Identification of Patent for which Extension Is Being Sought by Name of Inventor, Patent number, Date of Issue, and Date of Expiration (37 C.F.R. § 1.740(a)(6)).

The patent for which extension of patent term is sought is U.S. Patent No. 5,856,336 ("the '336 patent"), which names Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita and Masaki Kitahara as inventors, and which issued on January 5, 1999, from U.S. Patent Application Serial No. 07/883,398, and is currently set to expire on January 5, 2016.

VII. Copy of Patent for which Extension Is Being Sought (37 C.F.R. § 1.740(a)(7)).

A copy of the '336 patent is attached hereto as Exhibit B.

VIII. Copy of Any Disclaimer, Certificate of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate Issued in Patent (37 C.F.R. § 1.740(a)(8)).

Applicant states on the record that no disclaimers have been filed in the '336 patent, no certificates of correction have been requested or issued in the '336 patent, and no reexamination certificate has been issued in the '336 patent.

A copy of the receipts of maintenance fee payments for the first and second maintenance fees in the '336 patent are attached hereto as Exhibit C.

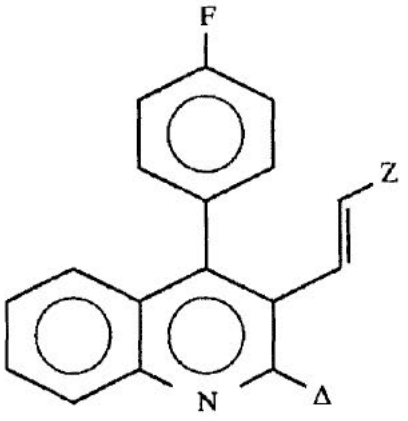
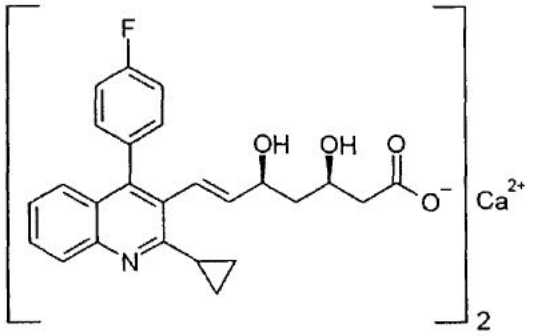
IX. Statement that Patent Claims Approved Product and Showing which Lists Each Applicable Patent Claim and Demonstrates Manner in which at least One Such Patent Claim Reads On Approved Product (37 C.F.R. § 1.740(a)(9)).

The approved product, Livalo®, film-coated tablets of pitavastatin calcium, is claimed in the '336 patent.

The relationship between the claims of the '336 patent and the approved product is set

forth in TABLE 1 below.

TABLE 1

Claims of the '336 Patent	Livalo®
1. A compound of the formula,  [A] Z= –CH(OH)–CH_2–CH(OH)–CH_2–COO·½ Ca.	Livalo® contains pitavastatin calcium, which is given by the formula  which is equivalent to the formula set forth in claim 1 of the '336 Patent.
2. A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in claim 1.	Livalo® is approved for administration to patients with primary hyperlipidemia.

X. **Statement Beginning on New Page of Relevant Dates and Information to Enable the Secretary of Health and Human Services to Determine Applicable Regulatory Review Period (37 C.F.R. § 1.740(a)(10)(i)).**

(A) Effective Date of Investigational New Drug (IND) Application and IND Number (37 C.F.R. § 1.740(a)(10)(i)(A)).

The effective date for the IND for the approved product is June 9, 2000, and the IND number for the approved product is IND 60,492.

(B) Date on which New Drug Application (NDA) was Initially Submitted and NDA Number (37 C.F.R. § 1.740(a)(10)(B)).

The NDA for the approved product was initially submitted on October 1, 2008, and the NDA number for the approved product is NDA 022363.

(C) Date on which NDA Was Approved (37 C.F.R. § 1.740(a)(10)(C)).

NDA 022363 was approved on August 3, 2009.

XI. Brief Description Beginning on New Page of Significant Activities Undertaken by Marketing Applicant during Applicable Regulatory Review Period with respect to Approved Product and Significant Dates Applicable to Such Activities (37 C.F.R. § 1.740(11)).

A. The IND.

A list of significant activities undertaken by the marketing applicant during the IND and the significant dates applicable thereto is provided in TABLE 2 below.

TABLE 2

DATE	TYPE	DESCRIPTION
6/9/00	Initial IND	22 Toxicology Reports, 1 Clinical Study Protocol (Study NK-104-101) to be Conducted in France
6/13/00	Correspondence	IND Acknowledgment Letter
6/14/00	Information Amendments	Form FDA 1572 and Revised Investigators' CV for Study NK-104-101
6/15/00	Other	Additional Copy of Volume 1.1 from the Initial IND Submission SN 0000
6/21/00	Other	Electronic Media for Original IND (2 Floppy Disks, 1 CD-ROM)
6/30/00	Correspondence	Copies of Pharmacology Publications
7/11/00	Teleconference	IND Comments Before the End of the 30-day Waiting Period
7/19/00	Teleconference	Follow-Up to Teleconference with Drs. Orloff and Lubas on 7/11/00
8/28/00	Correspondence	Meeting Minutes of the FDA Center for Drug Evaluation and Research, Executive Carcinogenesis Assessment Committee (FAX)

DATE	TYPE	DESCRIPTION
8/29/00	Correspondence	Meeting Minutes of the FDA Center for Drug Evaluation and Research, Executive Carcinogenesis Assessment Committee (official letter & minutes)
9/15/00	General Correspondence	Questions Regarding Carcinogenicity Studies
9/28/00	Other	Request for a Meeting with the Executive Carcinogenicity Assessment Committee
10/5/00	Correspondence	Telephone Conference with Pharm/Tox Team Confirmation
10/10/00	Correspondence	List of participants for teleconference on Oct. 11, 2000 for Carcinogenicity Studies
10/11/00	Teleconference	Carcinogenicity Issues
10/27/00	Correspondence	Minutes of the Telephone Conference on 10/11/00
10/27/00	Other	Sponsor Response to FDA Comments Regarding Slit Lamp Examinations in Multiple-Dose Clinical Studies
12/4/00	Other	Questions Regarding Survival Analysis of the 92-Week Mouse Study
12/12/00	Correspondence	Comments from Clinical Team Meeting
12/14/00	Correspondence	Information on Survival-Adjusted Analyses of Tumor Data
4/3/01	Protocol Amendments	Study Protocol for Study NK-104-209, Study NK-104-209 Investigator Information, Updated Investigators' Brochure (Feb 2001)
4/9/01	Teleconference	Comments about 4/3/01 Submission for 104-209 Protocol
4/23/01	Protocol Amendments	Study NK-104-209 Protocol Amendment (addition of Slit Lamp Examinations)
4/25/01	Information Amendments	Information Amendment: Clinical Data from Study NK-104-101 to Support 64-mg Dose Group in Study NK-104-209
5/15/01	Correspondence	Comments from the Clinical and Pharm/Tox Teams Regarding IND 60,492

DATE	TYPE	DESCRIPTION
5/31/01	Correspondence	Pharmacokinetic Data for Chronic Toxicity Studies
6/1/01	Correspondence	Pharmacokinetic Data for Chronic Toxicity Studies
6/4/01	Protocol Amendments	Study NK-104-209 Investigator Information
6/8/01	Information Amendments	Copies of a Monkey and a Rat Toxicokinetic Report (originally submitted as part of SN0000) requested by FDA
6/15/01	Other	NDA Questions
6/28/01	Information Amendments	Peer Review of Rat Carcinogencity Study Requested by FDA
6/29/01	Other	New Sponsor Liaison Person
6/17/01	IND Safety Reports	Study NK-104-209:Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial)
7/11/01	Teleconference	Termination of Randomization of Patients to 32 mg and 64 mg NK-104 and NK-104-209
7/12/01	Teleconference	Termination of Randomization of Patients to 32 mg and 64 mg NK-104 and NK-104-209 follow up with FDA
7/20/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial)
7/24/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial)
7/30/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial)
8/1/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial)
8/23/01	Protocol Amendments	Study NK-104-209 Amendment #2

DATE	TYPE	DESCRIPTION
8/24/01	Protocol Amendments	Study NK-104-209 Investigator Information
9/6/01	Other	Termination of Clinical Study NK-104-209
9/10/01	Annual Report	Annual Report IND 60,492 (7/12/00 - 7/11/01); CD-ROM
9/28/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Follow-Up #1; 2 patients)
10/30/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Follow-Up #2)
10/31/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Follow-Up #1)
12/14/01	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Follow-Up #1; 2 patients)
1/9/02	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Follow-Up #1)
2/11/02	IND Safety Reports	Study NK-104-209: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Follow-Up #2)
7/1/02	Protocol Amendments	Study NK-104-109 Protocol (Protocol Amendment #2), Study NK-104-109 Investigator Information
7/5/02	Protocol Amendments	Study NK-104-210 Protocol (Protocol Amendment #2), Investigator Information
9/17/02	Annual Report	Annual Report IND 60,492 (7/12/01 - 7/11/02)
10/4/02	Correspondence	Clinical Trials Data Bank
11/8/02	Protocol Amendments	Study NK-104-211 Protocol, Investigator Information

DATE	TYPE	DESCRIPTION
12/20/02	Other	Termination of Patients on 8 mg NK-104 in Study NK-104-210
2/25/03	Protocol Amendments	Study NK-104-210 Protocol Amendment #3 and #4)
9/16/03	Information Amendments	Study NK-104-109 Clinical Study Report, Study SNY 419/013926 Clinical Study Report
9/16/03	Annual Report	Annual Report (July 12, 2002 to July 11, 2003)
1/27/04	Teleconference	FDA suggested that Sankyo re-analyze the Phase I data in the NK-104-109 study and begin to think about an EOP2a meeting.
2/3/04	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Report - IND Safety Report - Initial
4/2/04	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Reports - 15-day expedited report - Initial
4/19/04	Information Amendments	Study NK-104-GJ Clinical Study Report, Study NKS104A2204 Clinical Study Report
6/1/04	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Reports - IND Safety Report - Initial (2 patients)
6/22/04	IND Safety Reports	Japan, Post-Marketing: Serious, Adverse Event Report - IND Safety Report - Follow-up No. 1
7/29/04	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Reports - IND Safety Report - Initial
9/10/04	Annual Report	Annual Report (July 12, 2003 to July 11, 2004)
9/23/04	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Reports - IND Safety Report - Initial

DATE	TYPE	DESCRIPTION
11/8/04	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Reports - IND Safety Report - Initial
12/14/04	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Report - IND Safety Report - Initial
1/21/05	Information Amendments	Study NK104-210/211 Clinical Study Report, Study NK104-101 Clinical Study Report
2/1/05	Information Amendments	Drug Product Stability Update
3/3/05	Information Amendments	Study NK-104-209 Clinical Study Report
3/23/05	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Report - IND Safety Report - Initial {Kowa comment: this has subsequently been identified as a follow-up report to SN046}
3/30/05	Other	Transfer of IND Ownership from Sankyo to KRI
3/31/05	Other	Acceptance from Sankyo of IND Ownership by KRI
3/31/05	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Report - IND Safety Report - Initial and follow-up #1 (last submission by Sankyo)
4/12/05	Correspondence	Transfer of Sponsor-Sankyo
4/18/05	IND Safety Report	Japan, Post-Marketing: Serious, Unexpected Adverse Event Report - IND Safety Report - Initial (First Submission by KRI)
4/25/05	IND Safety Report	Study NK-104: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial)

DATE	TYPE	DESCRIPTION
5/13/05	IND Safety Report	Study NK-104: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial), Japan, Post-Marketing Serious, Unexpected Adverse Event Report - IND Safety Report - Follow-up #1
6/1/05	IND Safety Report	Study NK-104: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial), Japan, Post-Marketing Serious, Unexpected Adverse Event Report - IND Safety Report - Follow-up #1
7/18/05	Other	End-of-Phase II Meeting Request
7/21/05	IND Safety Reports	Study NK-104: Serious, Unexpected Adverse Event Report – 15-Day Expedited Report (Initial), Japan, Post-Marketing Serious, Unexpected Adverse Event Report - IND Safety Report - Follou-up #1
7/26/05	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Report - IND Safety Report - Initial (First Submission by KRI)
7/29/05	Correspondence	EoP 2 Mtg Req Granted
8/4/05	IND Safety Reports	Japan, Post-Marketing: Serious, Unexpected Adverse Event Report - IND Safety Report - Initial (First Submission by KRI)
8/19/05	Other	End of Phase 2 Meeting Background Package
8/23/05	General Correspondence	New Company Point of Contact
9/2/05	IND Safety Reports	1 initial 3 follow-ups reports
9/9/05	Annual Report	Annual Report Document
9/14/05	Other	End-of-Phase II CMC Meeting Request
9/16/05	Information Amendments	Statistical Analysis Report
9/27/05	Information Amendments	Tox 078

DATE	TYPE	DESCRIPTION
9/28/05	Correspondence	EoP 2 Mtg Req 11-29-05
10/18/05	IND Safety Reports	Initial Written Report
10/25/05	Other	End of Phase 2 Meeting (CMC Focus)-Background Document
10/27/05	Information Amendments	Request for Division/ECAC Evaluation of Carcinogenicity Data
11/1/05	Correspondence	EoP-2 MtgMinutes of 9-20-05
11/30/05	IND Safety Reports	Initial Written Report
12/8/05	Correspondence	Kowa QA Meeting Cancellation Letter, EOP2 CMC response
1/3/06	Correspondence	Correction Letter
1/17/06	Correspondence	SN0073 White Paper
2/1/06	Information Amendments	Information Amendment: Clinical Response to EOP 2 Meeting Minutes
3/1/06	Correspondence	SN0075 Proteinuria
3/9/06	Other	Request for Type B Meeting - Phase 3 Guidance
3/10/06	IND Safety Reports	2 Initial and 3 follow-up reports
3/15/06	Correspondence	Mtg Rqt Denied Letter NK-104
3/21/06	Other	Background Information for FDA Response to Questions
3/27/06	New Protocol	protocol NK-104-1.21, Mar, 2006 IB
3/31/06	New Protocols	9 EU Phase 3 protocols
4/4/06	New Protocol	protocol NK-104-1.22
5/5/06	IND Safety Reports	Initial Report of Adverse Event; Follow-Up Reports of Adverse Events.
5/12/06	Protocol Amendments	protocol NK-104-1.25
6/1/06	Correspondence	SN0078
6/1/06	Correspondence	SN0080
6/27/06	IND Safety Reports	NK-104-0051 Initial ReportFollow-up Reports:ELIVA 3598 follow-up #2ELIVA 2657ELIVA 3873 follow-up #1 and #2

DATE	TYPE	DESCRIPTION
6/29/06	IND Safety Reports	2 Initial and 1 follow-up reportsELIVA 3338 and ELIVA 4169 Initial ReportsNK-104-0051 follow up report #1
7/10/06	IND Safety Reports	ELIVA 1532 Initial Report
8/4/06	IND Safety Reports	ELIVA 4374 Initial ReportFollow Up Reports:ELIVA 2657ELIVA 3338ELIVA 4168ELIVA 1854NK-104-0051
8/9/06	IND Safety Reports	ELIVA 1968
8/11/06	Protocol Amendments	NK-104-1.23, NK-104-1.25
8/30/06	IND Safety Reports	NK-104-0061
9/8/06	IND Safety Reports	A2006 1676-001 Initial Report2A2006 0040.005 follow-up #21A2005 0562.003 follow-up #1NK-104-0061 follow-up #1
9/22/06	Protocol Amendments	Nk-104-1.23US, Amend #2
9/27/06	IND Safety Reports	A2006 1773.001
10/3/06	Protocol Amendments	NK-104-1.23US, Amend #2
10/17/06	IND Safety Reports	NK-1040073 Initial ReportA20061773-002 follow-upA20061676-002 follow-up
10/26/06	Information Amendment	104 IV.102 EU; SPH003; SPH008
10/30/06	IND Annual Report	July 12, 2005-July 11, 2006
11/3/06	Special Protocol Assessment	rasH2 carcinogenicity protocol
11/14/06	IND Safety reports	A2006 1939-001 initial; 10001.2006.USNK104, initial; ELIVA 4374, F/U 1; A2006 1773.003/004 F/U 2&3; NK-104-0073 F/U 1
12/6/06	IND Safety Reports	ELIVA 2001/A20060643 initial & F/U; 10001.2006.USNK104 F/U
12/13/06	Correspondence	CAC Report 12-13-06 NK-104 Spec Protocol Assess
12/27/06	Response to FDA request	Response to FDA comments on SAPs for NK-104-301 and NK-104-302
1/23/07	IND Safety reports	1 initial (A2007-0046-001), 6 F/U

DATE	TYPE	DESCRIPTION
1/25/07	Correspondence	Comments from Dec 27, 2006 Serial #101 Letter
3/2/07	IND Safety reports	Initial Written Report(20070173-003)
4/10/07	Request for FDA Review/Comment	QTc Draft Protocol
4/13/07	IND Safety Report	A20070390-001/002- Initial & F/U & Medical Review & Analysis of Similar Events
5/8/07	Information Amendment	English translation of Japanese NDA clinical summary
5/11/07	IND Safety Reports	IND Safety Reports (1 initial and 2 F/U) A20070545-001/002, A20070390-003 #3, A20078070173-005 #2
5/29/07	Correspondence	Comments from April 10, 2007 Serial #104 Letter
5/30/07	IND Safety Reports	A20070589-002 A20070545-003, follow-up report #2
6/12/07	Request for FDA Review/Comment	Proposed Trade Name - Request for FDA Opinion (Livalo®)
6/26/07	New Protocol	NK-104-1.34US/Thomas Hunt, MD
7/23/07	IND Safety Report	NK-104-0190 Initial
8/17/07	IND Safety Reports	2 initial, A20070777 & A20070780 ; 2 F/U NK-104-0190 & A20060092
9/4/07	IND Safety Report	1 initial, A20070778
9/11/07	IND Safety Reports	4 initial, NK-104-205, NK-104-207, A20070806, A20070777: 1 F/U, A20070780
9/20/07	Annual Report	July 12, 2006-July 11, 2007
9/24/07	Information Ammendment	MET 067; SPH 011; SPH 012
10/4/07	Request for FDA Review/Comment	Request for Type B Meeting - FDA Pre-NDA Guidance Meeting Clinical and Nonclinical
10/25/07	Correspondence	NK-104 pre-NDA Meeting Confirm

DATE	TYPE	DESCRIPTION
11/15/07	Information Amendment	Vol 1 - NK-104-1.21US, NK-104-1.22US, NK-104-1.25US, NK-104-301 Vol 2 - NK-104-302, NK104--304, and NK-104-306
12/6/07	Pre-NDA Meeting Background document	Meeting Jan 28, 2008
12/7/07	Information Amendment	MET073 FBM06-T350FR
12/14/07	IND Safety Reports	NK-104-0190 follow-up report #4, A20070777-003/004 follow-up reports #3 and #4 and A20070806-002/003 reports #2 and #3
12/20/07	IND Safety Reports	A20070918-001 for a case of oculomucocutaneous syndrome reported with Livalo®, In addition one follow-up report is enclosed for NK-104-205, a case of macula hole previously reported in SN0114, which has been downgraded.
1/2/08	IND Safety Report	A20070901-002 for a case of renal impairment reported with Livalo®, (A20070901-001), is also included
2/27/08	Correspondence	FDA Pre-NDA Meeting Mins
4/4/08	New Protocol	Protocol for US study NK-104-1.37US , Also enclosed is a form FDA 1572 and CV for the Principal Investigator, Dr. Aziz Laurent as well as a transfer of obligations statement to the CRO, PPD Development LLP
4/8/08	Response to FDA request for Information	Pre-NDA meeting held January 28, 2008 Data Definition Table (DDT)
4/15/08	Correspondence	Pre NDA Meeting Follow-up Comment Received April 15, 2008
4/16/08	General Correspondence	RESPONSE REQUESTED – PRE-NDA MEETING CMC FOLLOW-UP
4/30/08	Correspondence	Pre-NDA Response FDA 4-30-2008 (SN0126)
5/13/08	IND Safety Report	A20070918-003 follow-up to A20070918-001

DATE	TYPE	DESCRIPTION
5/27/08	IND Safety Report	A20080109-001, for a case of obliterative bronchiolitis
9/9/08	Annual Report	July 12, 2007-July 11, 2008
9/24/08	IND Safety Reports	A20080109-002, A20070918-005 follow ups
9/30/08	General Correspondence	Notification of NDA
12/2/08	Correspondence	Trade Name
4/28/09	IND Initial Safety Report	NK-104 Initial Safety Report, Amendment SN0132
6/4/09	IND Safety Reports	Initial and Follow-up Safety Reports for A20090445-001 & A20090208-003
7/9/09	FDA Meeting Request	Combo FDA Guidance Meeting Request
8/11/09	IND Safety Report	A20090699-001, myocardial infarction

B. The NDA.

A list of significant activities undertaken by the marketing applicant during the NDA and the significant dates applicable thereto is provided in TABLE 3 below.

TABLE 3

DATE	TYPE	DESCRIPTION
10/1/08	Initial NDA	Initial NDA including fact sheet as background for proposed trade name, summary table which identifies important IND correspondence between Kowa and FDA, tabular listing of all IND submissions under IND 60,492, Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank
10/8/08	Correspondence	Acknowledgement
11/21/08	NDA Amendments	Clinical
11/26/08	NDA Amendments	Data Sets, with Two Pre-Clinical Carcinogenic studies
11/26/08	NDA Amendments	Coding dictionary SAS
12/2/08	Correspondence	Trade Name
12/12/08	NDA Amendments	Statistics-define
12/15/08	Correspondence	Filing
1/5/09	Correspondence	Clinical Pharmacology
1/14/09	NDA Amendments	LIVS-01 analysis
1/20/09	NDA Amendments	QTc study data
1/23/09	NDA Amendments	Revised Package Insert and labels
1/26/09	NDA Amendments	Rhabdomyolysismyopathy issues
1/30/09	NDA Amendments	NDA filing letter reponse -CMC and DMF change

DATE	TYPE	DESCRIPTION
2/6/09	NDA Amendments	Clincal pharmacology
2/6/09	NDA Amendments	CMC-Packaging
2/16/09	NDA Amendments	Safety Update
2/20/09	NDA Amendments	SNBL F-U
2/20/09	NDA Amendments	QTc F-U
3/6/09	NDA Amendments	Clinical AST-ALT
3/6/09	NDA Amendments	Clinical--JP AST-ALT
3/9/09	NDA Amendments	QTc F-U #2
3/9/09	NDA Amendments	SNBL F-U #2
3/10/09	NDA Amendments	Blister Sample labels
3/11/09	NDA Amendments	Re-analysis of Table 2.7.4.152
3/11/09	NDA Amendments	Response to request separate the 9 cases of rhabdomyolysis in table
3/11/09	NDA Amendments	Response to request to conduct a demographic analysis on the 37 post marketing cases of rhabdomyolysis in Japan
4/1/09	NDA Amendments	Response to FDA CMC comments
4/14/09	NDA Amendments	Response to e-mail from Kati Johnson regarding request from Manoj Khurana
4/16/09	NDA Amendments	Japan post marketing narratives (CIOMS) regarding previous e-mail request from Dr. Chowdhury
4/23/09	NDA Amendments	Response to e-mail from Kati Johnson regarding revised stability table
4/30/09	NDA Amendments	Response to e-mail from Kati Johnson conveying request from Dr. Chowdhury re: datasets
4/30/09	NDA Amendments	Initial Safety Report (A20090208-001) for a case of erythema multiforme exudativum submitted to IND SN0132
5/5/09	NDA Amendments	Response to a February 11, 2009 request for information (Modules 5.3.5 and 5.3.6)

DATE	TYPE	DESCRIPTION
5/7/09	NDA Amendments	Response to an April 29, 2009 e-mail from Dr. David Gortler re: questions about clinical study report
6/8/09	NDA Amendments	Response to clarification requests from Dr, Chowdhury May 22, 2009
6/8/09	NDA Amendments	Response to e-mail from Kati Johnson on May 27, 2009 request for location of ApoB identification
6/9/09	NDA Amendments	IND Safety Report (A20090208)
6/22/09	NDA Amendments	Response to June 9th e-mail from Dr. Chowdhury re: subjects in Group 1 and Group 3
7/6/09	NDA Amendments	Response to e-mail from Kati Johnson regarding Phase 4 Dissolution
7/7/09	NDA Amendments	Response to e-mail from Dr. Chowdhury's request for CRF's
7/13/09	NDA Amendments	Response to request to inform sponsor to retrieve 2 validation reports in english
7/27/09	NDA Amendments	Response to request for Group 1 CRF's
7/27/09	NDA Amendments	Response to request for laboratory values post 4/27/2007
8/3/09	Correspondence	NDA 022363 Approval

XII. Statement Beginning on New Page that in Opinion of Applicant Patent Is Eligible for Extension and Statement as to Length of Extension Claimed, Including How Length of Extension Was Determined (37 C.F.R. § 1.740(a)(12)).

In the opinion of the Applicant, the '336 patent is eligible for extension. In the opinion of the Applicant, the '336 patent is entitled to be extended by 1,826 days, i.e., the '336 patent is entitled to an extended expiration date of January 4, 2021. The extension was calculated by the method described in 37 C.F.R. § 1.775.

The number of days by which the '336 patent should be extended was calculated as follows:

A. The minimum number of days in the regulatory review period was calculated according to 37 C.F.R. § 1.775(c) and reduced as appropriate pursuant to 37 C.F.R. §§ 1.775(d)(1)-(6).

B. The minimum number of days in the regulatory review was calculated by adding the number of days pursuant to 37 C.F.R. § 1.775(c)(1) and the minimum number of days pursuant to 37 C.F.R. § 1.775(c)(2).

C. The number of days pursuant to 37 C.F.R. § 1.775(c)(1) was calculated as the number of days in the period starting from the date on which IND 60,492 was submitted, June 9, 2000, and ending on the date NDA 022363 was submitted, October 1, 2008, and determined to be at least 3,037 days.

D. The minimum number of days pursuant to 37 C.F.R. § 1.775(c)(2) was calculated as the number of days in the period starting from the date NDA 022363 was submitted, October 1, 2008, and ending on the date of approval of NDA 022363, August 3, 2009, and determined to be at least 307 days.

E. Thus, the minimum number of days in the regulatory review was calculated by adding 3,037 days to 307 days and determined to be 3,344 days

F. The number of days to be subtracted from the regulatory review period under 37 C.F.R. § 1.775(d)(1) was calculated by determining the number of days pursuant to each of 37 C.F.R. §§ 1.775(d)(1)(i)-(iii).

G. Since the regulatory review period began on June 9, 2000, and since the '336 patent issued on January 5, 1999, 0 days in the regulatory review period were on or before the date on which the '336 patent issued. Thus, the number of days pursuant to 37 C.F.R. § 1.775(d)(1)(i) was determined to be 0.

H. As set forth above, Applicants has acted with due diligence during the entire regulatory review period. Thus, the number of days pursuant to 37 C.F.R. § 1.775(d)(1)(ii) was determined to be 0.

I. The number of days pursuant to 37 C.F.R. § 1.775(d)(1)(iii) was calculated by first subtracting the number of days pursuant to 37 C.F.R. §§ 1.775(d)(1)(i) and 1.775(d)(1)(ii), 0 days, from the number of days pursuant to 37 C.F.R. § 1.775(c)(1), 3,037 days, to obtain 3,037 days and then dividing that number of day in half and determined to be 1,518 days.

J. The number of days pursuant to 37 C.F.R. § 1.775(d)(1) was calculated by subtracting the number of days calculated pursuant to 37 C.F.R. §§ 1.775(d)(1)(i) and 1.775(d)(1)(ii), 0 days, and the number of days calculated pursuant to 37 C.F.R. § 1.775(d)(1)(iii), 1,518 days, from the number of days calculated pursuant to 37 C.F.R. § 1.775(c), 3,344 days, and determined to be 1,826 days.

K. The term of the '336 patent as extended as determined by 37 C.F.R. § 1.775(d)(2) was calculated by adding the number of days calculated pursuant to 37 C.F.R. § 1.775(d)(1),

1,826 days, to the original term of the '336 patent (current expiration date January 5, 2016) and determined to be January 4, 2021.

L. The term of the '336 patent as extended as determined by 37 C.F.R. § 1.775(d)(3) was calculated by adding 14 years to the date of approval, August 3, 2009, and determined to be August 3, 2023.

M. The term of the '336 patent as extended as determined by 37 C.F.R. § 1.775(d)(4) was calculated by comparing the dates calculated pursuant to 37 C.F.R. § 1.775(d)(3) and 37 C.F.R. § 1.775(d)(4) and selecting the earlier date and determined to be January 4, 2021.

N. The term of the '336 patent as extended as determined by 37 C.F.R. § 1.775(d)(5)(i) was calculated by adding five years to the original expiration date of the '336 patent (January 5, 2016) and determined to be January 5, 2021.

O. The term of the '336 patent as extended as determined by 37 C.F.R. § 1.775(d)(5)(ii) was calculated by selecting the earlier date pursuant to 37 C.F.R. § 1.775(d)(4) and 37 C.F.R. § 1.775(d)(5)(i) and determined to be January 4, 2021.

P. Since the '336 patent issued after September 24, 1984, no adjustment was made under 37 C.F.R. § 1.775(d)(6).

XIII. Statement that Applicant Acknowledges Duty to Disclose to Director of United States Patent and Trademark Office and Secretary of Health and Human Services Any Information which Is Material to Determination of Entitlement to Extension Sought (37 C.F.R. §§ 1.740(a)(13) and 1.765).

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

It is understood that the duty of candor and good faith toward the Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture rests on the patent owner or its agent, on each attorney or agent who represents the patent owner and on every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding. All such individuals who are aware, or become aware, of material information adverse to a determination of entitlement to the extension sought, which has not been previously made of record in the patent term extension proceeding must bring such information to the attention of the Office or the Secretary, as appropriate, as soon as it is practical to do so after the individual becomes aware of the information. Information is material where there is a substantial likelihood that the Office or the Secretary would consider it important in determinations to be made in the patent term extension proceeding. 37 C.F.R. § 1.765(a).

It is also understood that disclosures pursuant to this section must be accompanied by a copy of each written document which is being disclosed. The disclosure must be made to the Office or the Secretary, as appropriate, unless the disclosure is material to determinations to be made by both the Office and the Secretary, in which case duplicate copies, certified as such,

must be filed in the Office and with the Secretary. Disclosures pursuant to this section may be made to the Office or the Secretary, as appropriate, through an attorney or agent having responsibility on behalf of the patent owner or its agent for the patent term extension proceeding or through a patent owner acting on his or her own behalf. Disclosure to such an attorney, agent or patent owner shall satisfy the duty of any other individual. Such an attorney, agent or patent owner has no duty to transmit information which is not material to the determination of entitlement to the extension sought. 37 C.F.R. § 1.765(b).

It is further understood that no patent will be determined eligible for extension and no extension will be issued if it is determined that fraud on the Office or the Secretary was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence in connection with the patent term extension proceeding. If it is established by clear and convincing evidence that any fraud was practiced or attempted on the Office or the Secretary in connection with the patent term extension proceeding or that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the patent term extension proceeding, a final determination will be made that the patent is not eligible for extension. 37 C.F.R. § 1.765(c).

XIV. Prescribed Fee for Receiving and Acting upon Application for Extension (37 C.F.R. § 1.740(a)(14)).

The fee as prescribed in 37 C.F.R. § 1.20(j) is attached hereto in the from of a credit card form for the amount of $1,120.00.

XV. Name, Address, and Telephone Number of Person to Whom Inquiries and Correspondence Relating to Application for Patent Term Extension are to be Directed (37 C.F.R. § 1.740(a)(15)).

All inquiries and correspondence should be sent to:

Customer Number: 22850

Which corresponds to:

Oblon, Spivak, McClelland, Maier & Neustadt, LLP.
1940 Duke Street
Alexandria, VA 22314

Telephone: 703-413-3000
Facsimile: 703-413-2220

XVI. Patent Term Extension Applicant (M.P.E.P. § 2752).

This application is being made by Nissan Chemical Industries, Ltd. ("Nissan"), which is the owner of the '336 patent by way of an assignment recorded with the U.S. Patent and Trademark Office at reel 004960, frame 0609 and attached hereto as Exhibit D. The undersigned is authorized to act on behalf of Nissan as pertains to the '336 patent and this application for extension of patent term.

Nissan was not the marketing applicant before the Food and Drug Administration in IND 60,492 or NDA 022363. Sankyo Pharma Inc. (now Daiichi Sankyo, Inc.) ("Sankyo") was the marketing applicant in IND 60,492 from the time of filing until 2005. In 2005, Kowa Research Institute, Inc. ("KRI"), assumed ownership and became the marketing applicant in IND 60,492. In 2008, KRI filed NDA 022363 as the authorized agent of Kowa Company, Ltd. ("KCL"). KCL, through its authorized agent KRI, was the marketing applicant in NDA 022363 through

approval. Attached as Exhibit E is a letter from KRI to the U.S. Patent and Trademark Office authorizing Nissan to rely on the activities of the marketing applicants before the Food and Drug Administration in IND 60,492 and NDA 022363.

* * * *

In view of the foregoing, Applicant submits that the present patent is entitled to the requested extension of patent term, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Jacob A. Doughty
Registration No. 46,671

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)

Attachment:
Exhibits A to E

Exhibit A

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022363

NDA APPROVAL

Kowa Research Institute, Inc.
Agent for Kowa Company, Limited
Attention: Ross Laderman
Senior Director, Regulatory Affairs
430 Davis Drive, Suite 200
Morrisville, NC 27560

Dear Mr. Laderman:

Please refer to the new drug application (NDA) you submitted on behalf of Kowa Company, Limited, dated October 1, 2008, received October 3, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Livalo® (pitavastatin) Tablets, 1 mg, 2 mg, and 4 mg.

We acknowledge receipt of your submissions dated November 21 and 26 (2 submissions), and December 12, 2008, and January 5, 14, 20 (2 submissions), 23, 26, and 29, February 6 (2 submissions), 16 and 20 (2 submissions), March 5 (2 submissions), 9 (2 submissions), 10, and 11 (3 submissions), April 1, 14, 16, 23, 29, and 30, May 5, 6, and 29, June 8, (2 submissions), 9 and 22, and July 6, 7, 9, 13, and 27 (2 submissions), 2009.

This new drug application provides for the use of Livalo (pitavastatin) Tablets for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of

Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-363.**"

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-363.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS (PMRs) UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of increased pitavastatin exposure in patients with severe renal impairment or in patients being co-administered the combination of lopinavir and ritonavir that may predispose these patients to myopathy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of increased pitavastatin exposure in patients with severe renal impairment, or in patients being co-administered the combination of lopinavir and ritonavir, that may predispose these patients to myopathy.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1501-1. A clinical trial to assess the effect of severe renal impairment on pitavastatin pharmacokinetics.

The timetable you submitted on July 27, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	October 30, 2009
Study Completion Date:	October 30, 2010
Final Report Submission:	December 31, 2010

1501-2. A drug-drug interaction clinical trial to examine the effect of the combination of lopinavir/ritonavir on pitavastatin Cmax and AUC.

The timetable you submitted on July 27, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	October 30, 2009
Study Completion Date:	October 30, 2010
Final Report Submission:	December 31, 2010

Submit the protocols to your IND, with a cross-reference letter to this NDA. Please use the above PMR numbers (1501-1 and 1501-2), as appropriate, in any submission regarding these PMRs. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

MISCELLANEOUS

Sufficient stability data have been submitted to support a 24-month expiration date for blister presentations, and a 36-month expiration date for 90-count bottles of the 1-, 2-, and 4-mg tablets.

We note the chemistry, manufacturing, and controls postmarketing agreement that was described in your amendment dated July 6, 2009.

NDA 22-363 was not referred to an advisory committee for review. Because pitavastatin is the eighth statin approved and there were no new significant efficacy or safety issues identified during the review of the application, other than those already identified for the statin drug class, an advisory committee meeting was not considered necessary.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Physician package insert
Carton and immediate-container labeling:
-2 mg blister card
-2 mg blister carton
-4 mg blister card
-4 mg blister carton
-1 mg bottle label (90-count)
-2 mg bottle label (90-count)
-4 mg bottle label (90-count)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIVALO safely and effectively. See full prescribing information for LIVALO.

LIVALO (pitavastatin) Tablet, Film Coated for Oral use
Initial U.S. Approval: 2009

---RECENT MAJOR CHANGES---
None

---INDICATIONS AND USAGE---
LIVALO is a HMG-CoA reductase inhibitor indicated for:

- Patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) (1.1)

Limitations of Use (1.2):

- Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.
- Effect of LIVALO on cardiovascular morbidity and mortality has not been determined
- LIVALO has not been studied in patients with severe renal impairment (glomerular filtration rate < 30 mL/min/1.73 m^2), not yet on hemodialysis. LIVALO should not be used in patient population.
- LIVALO has not been studied with the protease inhibitor combination lopinavir/ritonavir. LIVALO should not be used with this combination of protease inhibitors
- LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias

---DOSAGE AND ADMINISTRATION---

- LIVALO can be taken with or without food, at any time of day (2.1)
  Dose Range: 1 mg to 4 mg once daily (2.1)
- **Primary hyperlipidemia and mixed dyslipidemia:** Starting dose 2 mg. When lowering of LDL-C is insufficient, the dosage may be increased to a maximum of 4 mg per day. (2.1)
- **Moderate renal impairment (glomerular filtration rate 30 < 60 mL/min/1.73 m^2) and end-stage renal disease on hemodialysis:** Starting dose of 1 mg once daily and maximum dose of 2 mg once daily (2.2)

---DOSAGE FORMS AND STRENGTHS---

- Tablets: 1 mg, 2 mg, and 4 mg (3)

---CONTRAINDICATIONS---

- Known hypersensitivity to product components (4)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)
- Co-administration with cyclosporine (4, 7.1, 12.3)

---WARNINGS AND PRECAUTIONS---

- **Skeletal muscle effects (e.g., myopathy and rhabdomyolysis):** Risks increase in a dose-dependent manner, with advanced age (>65), renal impairment, inadequately treated hypothyroidism, and combination use with fibrates. Advise patients to promptly report unexplained muscle pain, tenderness, or weakness, and discontinue LIVALO if signs or symptoms appear (5.1)
- **Liver enzymes abnormalities and monitoring:** Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment (5.2)

---ADVERSE REACTIONS---
The most frequent adverse reactions (rate ≥2.0% in at least one marketed dose) were myalgia, back pain, diarrhea, constipation and pain in extremity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Kowa Pharmaceuticals America, Inc. at (1-877-334-3464) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---DRUG INTERACTIONS---

- **Lopinavir/Ritonavir:** This combination should not be used with LIVALO (1.2, 7.2)
- **Erythromycin:** Combination increases pitavastatin exposure. Limit LIVALO to 1 mg once daily (2.3, 7.3)
- **Rifampin:** Combination increases pitavastatin exposure. Limit LIVALO to 2 mg once daily (2.4, 7.4)
- **Fibrates:** Use with fibrate products may increase the risk of adverse skeletal muscle effects (5.1, 7.5)

---USE IN SPECIFIC POPULATIONS---

- **Pediatric use:** Safety and effectiveness have not been established. (8.4)
- **Renal impairment:** Limitation of a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily for patients with moderate renal impairment and patients receiving hemodialysis (2.2, 8.6) Patients with severe renal impairment not receiving hemodialysis have not been studied. LIVALO should not be used in this patient population (5.1, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Drug therapy should be one component of multiple-risk-factor intervention in individuals who require modifications of their lipid profile. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate.

1.1 Primary Hyperlipidemia and Mixed Dyslipidemia

LIVALO is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

1.2 Limitations of Use

Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.

The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.

LIVALO has not been studied in patients with severe renal impairment (glomerular filtration rate < 30 mL/min/1.73 m^2) not on hemodialysis. LIVALO should not be used in this patient population.

LIVALO has not been studied with the protease inhibitor combination lopinavir/ritonavir. LIVALO should not be used with this combination of protease inhibitors.

LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The dose range for LIVALO is 1 to 4 mg orally once daily at any time of the day with or without food. The recommended starting dose is 2 mg and the maximum dose is 4 mg. The starting dose and maintenance doses of LIVALO should be individualized according to patient characteristics, such as goal of therapy and response.

After initiation or upon titration of LIVALO, lipid levels should be analyzed after 4 weeks and the dosage adjusted accordingly.

2.2 Dosage in Patients with Renal Impairment

Patients with moderate renal impairment (glomerular filtration rate 30 to < 60 mL/min/1.73 m^2) and end –stage renal disease receiving hemodialysis should receive a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily.
LIVALO should not be used in patients with severe renal impairment (glomerular filtration rate < 30 mL/min/1.73 m^2)

2.3 Use with Erythromycin

In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded *[Drug Interactions (7.3)]*.

2.4 Use with Rifampin

In patients taking rifampin, a dose of LIVALO 2 mg once daily should not be exceeded *[see Drug Interactions (7.4)]*.

3 DOSAGE FORMS AND STRENGTHS

1 mg: Round white film-coated tablet. Debossed "KC" on one side and "1" on the other side of the tablet.
2 mg: Round white film-coated tablet. Debossed "KC" on one side and "2" on the other side of the tablet.
4 mg: Round white film-coated tablet. Debossed "KC" on one side and "4" on the other side of the tablet.

4 CONTRAINDICATIONS

The use of LIVALO is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO *[see Adverse Reactions (6.1)]*.

- Patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, LIVALO may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.2)]*.
- Nursing mothers. Animal studies have shown that LIVALO passes into breast milk. Since HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, LIVALO, like other HMG-CoA reductase inhibitors, is contraindicated in pregnant or nursing mothers *[see Use in Specific Populations (8.3 and Nonclinical Toxicology (13.2)]*.
- Co-administration with cyclosporine *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3]*.

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including LIVALO. These risks can occur at any dose level, but increase in a dose-dependent manner.

LIVALO should be prescribed with caution in patients with predisposing factors for myopathy. These factors include advanced age (>65 years), renal impairment, and inadequately treated hypothyroidism. The risk of myopathy may also be increased with concurrent administration of fibrates or lipid-modifying doses of niacin. LIVALO should be administered with caution in patients with impaired renal function, in elderly patients, or when used concomitantly with fibrates or lipid-modifying doses of niacin *[see Drug Interactions (7.6), Use in Specific Populations (8.5, 8.6) and Clinical Pharmacology (12.3)]*.

LIVALO therapy should be discontinued if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. LIVALO therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Enzyme Abnormalities and Monitoring

Increases in serum transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMG-CoA reductase inhibitors, including LIVALO. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.

In placebo-controlled Phase 2 studies, ALT >3 times the upper limit of normal was not observed in the placebo, LIVALO 1 mg, or LIVALO 2 mg groups. One out of 202 patients (0.5%) administered LIVALO 4 mg had ALT >3 times the upper limit of normal.

It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose and periodically (e.g., semiannually) thereafter.

Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times upper limit of normal persist, reduction of dose or withdrawal of LIVALO is recommended.

As with other HMG-CoA reductase inhibitors, LIVALO should be used with caution in patients who consume substantial quantities of alcohol. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of LIVALO *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) *[see Warnings and Precautions (5.1)]*.
- Liver Enzyme Abnormalities *[see Warning and Precautions (5.2)]*.

Of 4,798 patients enrolled in 10 controlled clinical studies and 4 subsequent open-label extension studies, 3,291 patients were administered pitavastatin 1 mg to 4 mg daily. The mean continuous exposure of pitavastatin (1 mg to 4 mg) was 36.7 weeks (median

51.1 weeks). The mean age of the patients was 60.9 years (range; 18 years – 89 years) and the gender distribution was 48% males and 52% females. Approximately 93% of the patients were Caucasian, 7% were Asian/Indian, 0.2% were African American and 0.3% were Hispanic and other.

6.1 Clinical Studies Experience

Because clinical studies on LIVALO are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of LIVALO cannot be directly compared with that in the clinical studies of other HMG-CoA reductase inhibitors and may not reflect the frequency of adverse reactions observed in clinical practice.

Adverse reactions reported in ≥ 2% of patients in controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had treatment duration of up to 12 weeks.

Table 1. Adverse Reactions* Reported by ≥2.0% of Patients Treated with LIVALO and > Placebo in Short-Term Controlled Studies

Adverse Reactions*	Placebo N= 208	LIVALO 1 mg N=309	LIVALO 2 mg N=951	LIVALO 4 mg N=1540
Back Pain	2.9%	3.9%	1.8%	1.4%
Constipation	1.9%	3.6%	1.5%	2.2%
Diarrhea	1.9%	2.6%	1.5%	1.9 %
Myalgia	1.4%	1.9%	2.8%	3.1%
Pain in extremity	1.9%	2.3%	0.6%	0.9%

* Adverse reactions by MedDRA preferred term.

Other adverse reactions reported from clinical studies were arthralgia, headache, influenza, and nasopharyngitis.

The following laboratory abnormalities have also been reported: elevated creatine phosphokinase, transaminases, alkaline phosphatase, bilirubin, and glucose.

In controlled clinical studies and their open-label extensions, 3.9% (1 mg), 3.3% (2 mg), and 3.7% (4 mg) of pitavastatin-treated patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: elevated creatine phosphokinase (0.6% on 4 mg) and myalgia (0.5% on 4 mg).

Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO.

7 DRUG INTERACTIONS

7.1 Cyclosporine

Cyclosporine significantly increased pitavastatin exposure. Co-administration of cyclosporine with LIVALO is contraindicated [*see Contraindications (4), and Clinical Pharmacology (12.3)]*.

7.2 Lopinavir/Ritonavir

Based on data with another HMG-CoA reductase inhibitor that has a similar pharmacokinetic profile to that of pitavastatin, coadministration of the protease inhibitor combination, lopinavir/ritonavir, with LIVALO may significantly increase pitavastatin exposure. Therefore, LIVALO should not be used with this combination of protease inhibitors. [*see Limitations of Use (1.2)]*.

7.3 Erythromycin

Erythromycin significantly increased pitavastatin exposure. In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.4 Rifampin

Rifampin significantly increased pitavastatin exposure. In patients taking rifampin, a dose of LIVALO 2 mg once daily should not be exceeded *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

7.5 Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors may be increased with concurrent administration of fibrates, LIVALO should be administered with caution when used concomitantly with gemfibrozil or other fibrates *[see Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

7.6 Niacin
The risk of skeletal muscle effects may be enhanced when LIVALO is used in combination with niacin; a reduction in LIVALO dosage should be considered in this setting *[see Warnings and Precautions (5.1)]*.

7.7 Warfarin
LIVALO had no significant pharmacokinetic interaction with R- and S- warfarin. LIVALO had no significant effect on prothrombin time (PT) and international normalized ratio (INR) when administered to patients receiving chronic warfarin treatment *[see Clinical Pharmacology (12.3)]*. However, patients receiving warfarin should have their PT and INR monitored when pitavastatin is added to their therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic effects: Pregnancy Category X
LIVALO is contraindicated in women who are or may become pregnant. Serum cholesterol and TG increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy *[see Contraindications (4)]*.

There are no adequate and well-controlled studies of LIVALO in pregnant women, although, there have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Reproductive toxicity studies have shown that pitavastatin crosses the placenta in rats and is found in fetal tissues at ≤36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation.

Embryo-fetal developmental studies were conducted in pregnant rats treated with 3, 10, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. No adverse effects were observed at 3 mg/kg/day, systemic exposures 22 times human systemic exposure at 4 mg/day based on AUC.

Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1, 0.3, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

In perinatal/postnatal studies in pregnant rats given oral gavage doses of pitavastatin at 0.1, 0.3, 1, 3, 10, 30 mg/kg/day from organogenesis through weaning, maternal toxicity consisting of mortality at ≥0.3 mg/kg/day and impaired lactation at all doses contributed to the decreased survival of neonates in all dose groups (0.1 mg/kg/day represents approximately 1 time human systemic exposure at 4 mg/day dose based on AUC).

LIVALO may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking LIVALO, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers
It is not known whether pitavastatin is excreted in human milk, however, it has been shown that a small amount of another drug in this class passes into human milk. Rat studies have shown that pitavastatin is excreted into breast milk. Because another drug in this class passes into human milk and HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require LIVALO treatment should be advised not to nurse their infants or to discontinue LIVALO *[see Contraindications (4)]*.

8.4 Pediatric Use
Safety and effectiveness of LIVALO in pediatric patients have not been established.

8.5 Geriatric Use
Of the 2,800 patients randomized to LIVALO 1 mg to 4 mg in controlled clinical studies, 1,209 (43%) were 65 years and older. No significant differences in efficacy or safety were observed between elderly patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Patients with moderate renal impairment (glomerular filtration rate 30 to < 60 mL/min/1.73 m^2) and end-stage renal disease receiving hemodialysis should receive a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily*[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

LIVALO is contraindicated in patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels.

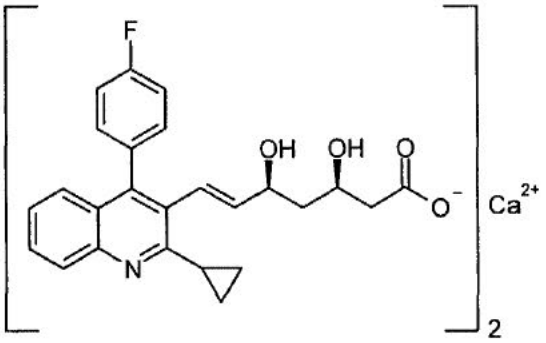
10 OVERDOSAGE

There is no known specific treatment in the event of overdose of pitavastatin. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis is unlikely to be of benefit due to high protein binding ratio of pitavastatin.

11 DESCRIPTION

LIVALO (pitavastatin) is an inhibitor of HMG-CoA reductase. It is a synthetic lipid-lowering agent for oral administration.

The chemical name for pitavastatin is (+)monocalcium *bis*{(3R, 5S, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}. The structural formula is:



The empirical formula for pitavastatin is $C_{50}H_{46}CaF_2N_2O_8$ and the molecular weight is 880.98. Pitavastatin is odorless and occurs as white to pale-yellow powder. It is freely soluble in pyridine, chloroform, dilute hydrochloric acid, and tetrahydrofuran, soluble in ethylene glycol, sparingly soluble in octanol, slightly soluble in methanol, very slightly soluble in water or ethanol, and practically insoluble in acetonitrile or diethyl ether. Pitavastatin is hygroscopic and slightly unstable in light.

Each film-coated tablet of LIVALO contains 1.045 mg, 2.09 mg, or 4.18 mg of pitavastatin calcium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of free base and the following inactive ingredients: lactose monohydrate, low substituted hydroxypropylcellulose, hypromellose, magnesium aluminometasilicate, magnesium stearate, and film coating containing the following inactive ingredients: hypromellose, titanium dioxide, triethyl citrate, and colloidal anhydrous silica.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins.

12.2 Pharmacodynamics

In a randomized, double-blind, placebo-controlled, 4-way parallel, active-comparator study with moxifloxacin in 174 healthy participants, LIVALO was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 16 mg (4 times the recommended maximum daily dose).

12.3 Pharmacokinetics

Absorption: Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. Both C_{max} and $AUC_{0\text{-}inf}$ increased in an approximately dose-proportional manner for single LIVALO doses from 1 to 24 mg once daily. The absolute bioavailability of pitavastatin oral solution is 51%. Administration of LIVALO with a high fat meal (50% fat content) decreases pitavastatin C_{max} by 43% but does not significantly reduce pitavastatin AUC. The C_{max} and AUC of pitavastatin did not differ following evening or morning drug administration. In healthy volunteers receiving 4 mg pitavastatin, the percent change from baseline for LDL-C following evening dosing was slightly greater than that following morning dosing. Pitavastatin was absorbed in the small intestine but very little in the colon.

Distribution: Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 148 L. Association of pitavastatin and/or its metabolites with the blood cells is minimal.

Metabolism:. Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. The major metabolite in human plasma is the lactone which is formed via an ester-type pitavastatin glucuronide conjugate by uridine 5'-diphosphate (UDP) glucuronosyltransferase (UGT1A3 and UGT2B7).

Excretion: A mean of 15% of radioactivity of orally administered single 32 mg ^{14}C-labeled pitavastatin dose was excreted in urine, whereas a mean of 79% of the dose was excreted in feces within 7 days. The mean plasma elimination half-life is approximately 12 hours.

Race: In pharmacokinetic studies pitavastatin C_{max} and AUC were 21 and 5% lower, respectively in Black or African American healthy volunteers compared with those of Caucasian healthy volunteers. In pharmacokinetic comparison between Caucasian volunteers and Japanese volunteers, there were no significant differences in C_{max} and AUC.

Gender: In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin C_{max} and AUC were 60 and 54% higher, respectively in females. This had no effect on the efficacy or safety of LIVALO in women in clinical studies.

Geriatric: In a pharmacokinetic study which compared healthy young and elderly (≥65 years) volunteers, pitavastatin C_{max} and AUC were 10 and 30% higher, respectively, in the elderly. This had no effect on the efficacy or safety of LIVALO in elderly subjects in clinical studies.

Renal Impairment: In patients with moderate renal impairment (glomerular filtration rate of 30 to <60 mL/min/1.73 m^2) and end stage renal disease receiving hemodialysis, pitavastatin $AUC_{0\text{-}inf}$ is 79 and 86% higher than those of healthy volunteers, respectively, while pitavastatin C_{max} is 60 and 40% higher than those of healthy volunteers, respectively. Patients received hemodialysis immediately before pitavastatin dosing and did not undergo hemodialysis during the pharmacokinetic study. Hemodialysis patients have 33 and 36% increases in the mean unbound fraction of pitavastatin as compared to healthy volunteers and patients with moderate renal impairment, respectively. The effect of mild and severe renal impairment on pitavastatin exposure is unknown.

Hepatic Impairment: The disposition of pitavastatin was compared in healthy volunteers and patients with various degrees of hepatic impairment. The ratio of pitavastatin C_{max} between patients with moderate hepatic impairment (Child-Pugh B disease) and healthy volunteers was 2.7. The ratio of pitavastatin AUC_{inf} between patients with moderate hepatic impairment and healthy volunteers was 3.8. The ratio of pitavastatin C_{max} between patients with mild hepatic impairment (Child-Pugh A disease) and healthy volunteers was 1.3. The ratio of pitavastatin AUC_{inf} between patients with mild hepatic impairment and healthy volunteers was 1.6. Mean pitavastatin $t_{½}$ for moderate hepatic impairment, mild hepatic impairment, and healthy were 15, 10, and 8 hours, respectively.

Drug-Drug Interactions: The principal route of pitavastatin metabolism is glucuronidation via liver UGTs with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system.

Warfarin: The steady-state pharmacodynamics (international normalized ratio [INR] and prothrombin time [PT]) and pharmacokinetics of warfarin in healthy volunteers were unaffected by the co-administration of LIVALO 4 mg daily. However, patients receiving warfarin should have their PT time or INR monitored when pitavastatin is added to their therapy.

Table 2. Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in C_{max}*
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8 fold †	↑ 3.6 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29%	↑ 2.0 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑18%	↑ 11%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2%	↓0.2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6%	↓ 7%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4%	↓ 9%
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice for 4 days	↑ 15%	↓ 12%
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days	↓ 23%	↓ 22%

*Data presented as x-fold change represent the ratio between co-administration and pitavastatin alone (i.e., 1-fold = no change). Data presented as % change represent % difference relative to pitavastatin alone (i.e., 0% = no change).
† Considered clinically significant *[see Dosage and Administration (2) and Drug Interactions (7)]*

Table 3. Effect of Pitavastatin Co-Administration on Systemic Exposure to Other Drugs

Co-administered drug	Dose regimen		Change in AUC*	Change in C_{max}*
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days		↑ 6%	↑ 13%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	Enalapril	↑ 12%	↑ 12%
		Enalaprilat	↓ 1%	↓ 1%
Warfarin	Individualized maintenance dose of warfarin (2 - 7 mg) for 8 days + pitavastatin 4 mg QD for 9 days	R-warfarin	↑ 7%	↑ 3%
		S-warfarin	↑ 6%	↑ 3%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days		↑ 9%	↑ 2%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days		↓ 3%	↓ 4%
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days		↓ 15%	↓ 18%

*Data presented as % change represent % difference relative to the investigated drug alone (i.e., 0% = no change).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
In a 92-week carcinogenicity study in mice given pitavastatin, at the maximum tolerated dose of 75 mg/kg/day with systemic maximum exposures (AUC) 26 times the clinical maximum exposure at 4 mg/day, there was an absence of drug-related tumors.

In a 92-week carcinogenicity study in rats given pitavastatin at 1, 5, 25 mg/kg/day by oral gavage there was a significant increase in the incidence of thyroid follicular cell tumors at 25 mg/kg/day, which represents 295 times human systemic exposures based on AUC at the 4 mg/day maximum human dose.

In a 26-week transgenic mouse (Tg rasH2) carcinogenicity study where animals were given pitavastatin at 30, 75, and 150 mg/kg/day by oral gavage, no clinically significant tumors were observed.

Pitavastatin was not mutagenic in the Ames test with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the micronucleus test following a single administration in mice and multiple administrations in rat, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In the chromosomal aberration test, clastogenicity was observed at the highest doses tested which also elicited high levels of cytotoxicity.

Pitavastatin had no adverse effects on male and female rat fertility at oral doses of 10 and 30 mg/kg/day, respectively, at systemic exposures 56- and 354-times clinical exposure at 4 mg/day based on AUC.

Pitavastatin treatment in rabbits resulted in mortality in males and females given 1 mg/kg/day (30-times clinical systemic exposure at 4 mg/day based on AUC) and higher during a fertility study. Although the cause of death was not determined, rabbits had gross signs of renal toxicity (kidneys whitened) indicative of possible ischemia. Lower doses (15-times human systemic exposure) did not show significant toxicity in adult males and females. However, decreased implantations, increased resorptions, and decreased viability of fetuses were observed.

13.2 Animal Toxicology and/or Pharmacology

Central Nervous System Toxicity
CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Wallerian degeneration has not been observed with pitavastatin. Cataracts and lens opacities were seen in dogs treated for 52 weeks at a dose level of 1 mg/kg/day (9 times clinical exposure at the maximum human dose of 4 mg/day based on AUC comparisons.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia or Mixed Dyslipidemia

Dose-ranging study: A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study was performed to evaluate the efficacy of LIVALO compared with placebo in 251 patients with primary hyperlipidemia (Table 4). LIVALO given as a single daily dose for 12 weeks significantly reduced plasma LDL-C, TC, TG, and Apo-B compared to placebo and was associated with variable increases in HDL-C across the dose range.

Table 4. Dose-Response in Patients with Primary Hypercholesterolemia (Adjusted Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C
Placebo	53	-3	-2	-2	1	0
LIVALO 1mg	52	-32	-25	-23	-15	8
LIVALO 2mg	49	-36	-30	-26	-19	7
LIVALO 4mg	51#	-43	-35	-31	-18	5

#The number of subjects for Apo-B was 49

Active-controlled study with atorvastatin (NK-104-301): LIVALO was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 817 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomized to a 12-week treatment with either LIVALO or atorvastatin (Table 5). Non-inferiority of pitavastatin to a given dose of atorvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 5. For the percent change from baseline to endpoint in LDL-C, LIVALO was non-inferior to atorvastatin for the two pairwise comparisons: LIVALO 2 mg vs. atorvastatin 10 mg and LIVALO 4 mg vs. atorvastatin 20 mg. Mean treatment differences (95% CI) were 0% (-3%, 3%) and 1% (-2%, 4%), respectively.

Table 5. Response by Dose of LIVALO and Atorvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 2 mg daily	315	-38	-30	-28	-14	4	-35
LIVALO 4 mg daily	298	-45	-35	-32	-19	5	-41
Atorvastatin 10 mg daily	102	-38	-29	-28	-18	3	-35
Atorvastatin 20 mg daily	102	-44	-36	-33	-22	2	-41
Atorvastatin 40 mg daily	----------Not Studied----------						
Atorvastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with simvastatin (NK-104-302): LIVALO was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 843 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomized to a 12 week treatment with either LIVALO or simvastatin (Table 6). Non-inferiority of pitavastatin to a given dose of simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 6. For the percent change from baseline to endpoint in LDL-C, LIVALO was non-inferior to simvastatin for the two pairwise comparisons: LIVALO 2 mg vs. simvastatin 20 mg and LIVALO 4 mg vs. simvastatin 40 mg. Mean treatment differences (95% CI) were 4% (1%, 7%) and 1% (-2%, 4%), respectively.

Table 6. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 2 mg daily	307	-39	-30	-28	-16	6	-36
LIVALO 4 mg daily	319	-44	-35	-32	-17	6	-41
Simvastatin 20 mg daily	107	-35	-27	-25	-16	6	-32
Simvastatin 40 mg daily	110	-43	-34	-31	-16	7	-39
Simvastatin 80 mg	----------Not Studied----------						

Active-controlled study with pravastatin in elderly (NK-104-306): LIVALO was compared with the HMG-CoA reductase inhibitor pravastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled non-inferiority Phase 3 study of 942 elderly patients (≥65 years) with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period, and then were randomized to a once daily dose of LIVALO or pravastatin for 12 weeks (Table 7). Non-inferiority of LIVALO to a given dose of pravastatin was assumed if the lower bound of the 95% CI for the treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 7. LIVALO significantly reduced LDL-C compared to pravastatin as demonstrated by the following pairwise dose comparisons: LIVALO 1 mg vs. pravastatin 10 mg, LIVALO 2 mg vs. pravastatin 20 mg and LIVALO 4 mg vs. pravastatin 40 mg. Mean treatment differences (95% CI) were 9% (6%, 12%), 10% (7%, 13%) and 10% (7%, 13%), respectively.

Table 7. Response by Dose of LIVALO and Pravastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 1 mg daily	207	-31	-25	-22	-13	1	-29
LIVALO 2 mg daily	224	-39	-31	-27	-15	2	-36
LIVALO 4 mg daily	210	-44	-37	-31	-22	4	-41
Pravastatin 10 mg daily	103	-22	-17	-15	-5	-0	-20
Pravastatin 20 mg daily	96	-29	-22	-21	-11	-1	-27
Pravastatin 40 mg daily	102	-34	-28	-24	-15	1	-32
Pravastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with simvastatin in patients with ≥ 2 risk factors for coronary heart disease (NK-104-304): LIVALO was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 351 patients with primary hyperlipidemia or mixed dyslipidemia with ≥2 risk factors for coronary heart disease. After a 6- to 8-week wash-out/dietary lead-in period, patients were randomized to a 12-week treatment with either LIVALO or simvastatin (Table 8). Non-inferiority of LIVALO to simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are show in Table 8. LIVALO 4 mg was non-inferior to simvastatin 40 mg for percent change from baseline to endpoint in LDL-C. The mean treatment difference (95% CI) was 0% (-2%, 3%).

Table 8. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia with ≥2 Risk Factors for Coronary Heart Disease (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 4 mg daily	233	-44	-34	-31	-20	7	-40
Simvastatin 40 mg daily	118	-44	-34	-31	-15	5	-39
Simvastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with atorvastatin in patients with type II diabetes mellitus (NK-104-305): LIVALO was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, non-inferiority Phase 3 study of 410 subjects with type II diabetes mellitus and combined dyslipidemia. Patients entered a 6- to 8-week washout/dietary lead-in period and were randomized to a once daily dose of LIVALO or atorvastatin for 12 weeks. Non-inferiority of LIVALO was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

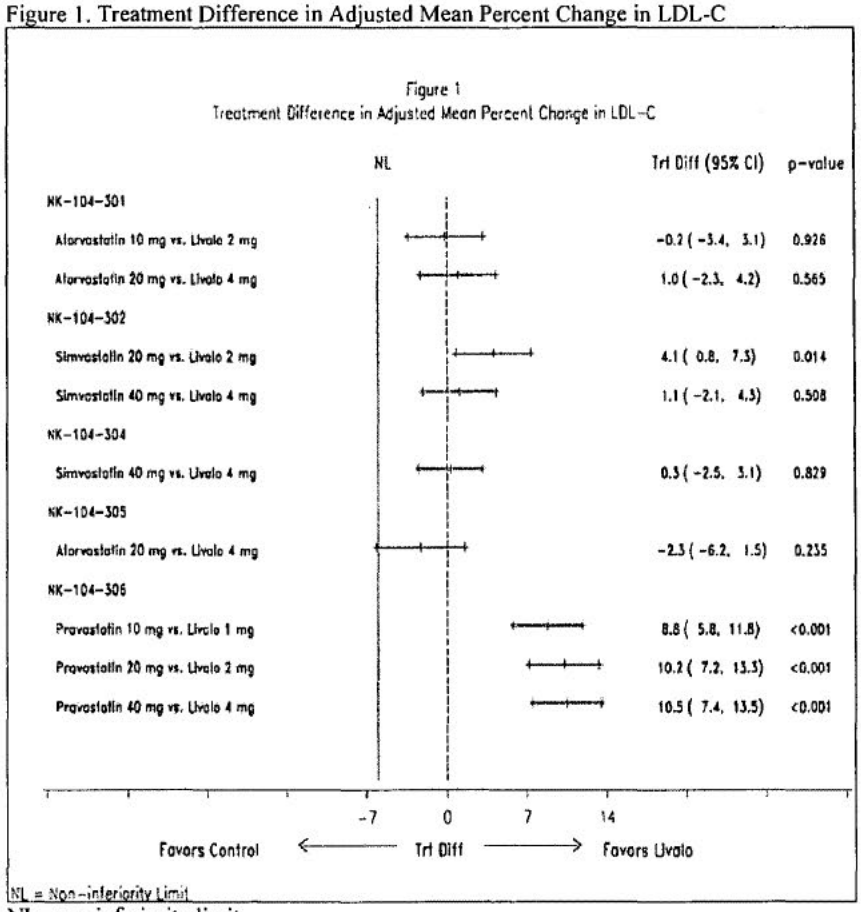
Lipid results are shown in Table 9. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%). The two treatment groups were not statistically different on LDL-C. However, the lower limit of the CI was -6.2%, slightly exceeding the -6% non-inferiority limit so that the non-inferiority objective was not achieved.

Table 9. Response by Dose of LIVALO and Atorvastatin in Patients with Type II Diabetes Mellitus and Combined Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 4 mg daily	274	-41 %	-32%	-28%	-20%	7%	-36
Atorvastatin 20 mg daily	136	-43 %	-34%	-32%	-27%	8%	-40
Atorvastatin 40 mg daily	----------Not Studied----------						
Atorvastatin 80 mg daily	----------Not Studied----------						

The treatment differences in efficacy in LDL-C change from baseline between LIVALO and active controls in the Phase 3 studies are summarized in Figure 1.

Figure 1. Treatment Difference in Adjusted Mean Percent Change in LDL-C



NL=non-inferiority limit.

15 HOW SUPPLIED/STORAGE AND HANDLING

LIVALO tablets for oral administration are provided as white, film-coated tablets that contain 1 mg, 2 mg, or 4 mg of pitavastatin. Each tablet has "KC" debossed on one side and a code number specific to the tablet strength on the other.

Packaging
LIVALO® (pitavastatin) Tablets are supplied as;

- NDCXXX: 1 mg. Round white film-coated tablet debossed "KC" on one face and "1" on the reverse; HDPE bottles of 90 tablets
- NDCXXX: 2 mg. Round white film-coated tablet debossed "KC" on one face and "2" on the reverse; HDPE bottles of 90 tablets
- NDCXXX: 4 mg. Round white film-coated tablet debossed "KC" on one face and "4" on the reverse; HDPE bottles of 90 tablets

Storage
Store at room temperature between 15°C and 30°C (59° to 86° F) [see USP]. Protect from light.

16 PATIENT COUNSELING INFORMATION

The patient should be informed of the following:

16.1 Dosing Time
LIVALO can be taken at any time of the day with or without food.

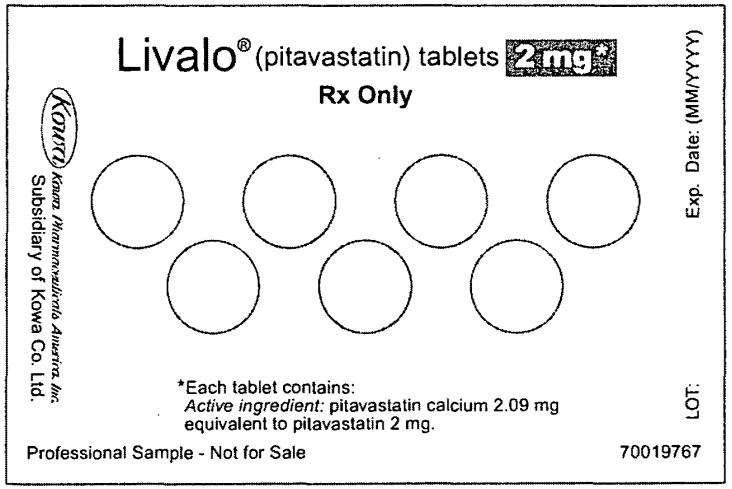
16.2 Muscle Pain
Patients should be advised to promptly notify their physician of any unexplained muscle pain, tenderness, or weakness. They should discuss all medication, both prescription and over the counter, with their physician.

16.3 Pregnancy
Women of childbearing age should use an effective method of birth control to prevent pregnancy while using LIVALO. Discuss future pregnancy plans with your healthcare professional, and discuss when to stop LIVALO if you are trying to conceive. If you are pregnant, stop taking LIVALO and call your healthcare professional.

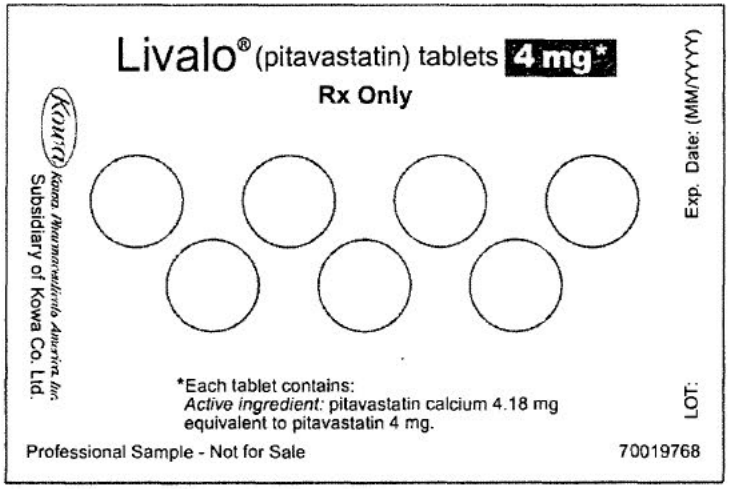
16.4 Breastfeeding
Women who are breastfeeding should not use LIVALO. If you have a lipid disorder and are breastfeeding, stop taking LIVALO and consult with your healthcare professional.

16.5 Liver Enzymes
It is recommended that liver enzymes be checked before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

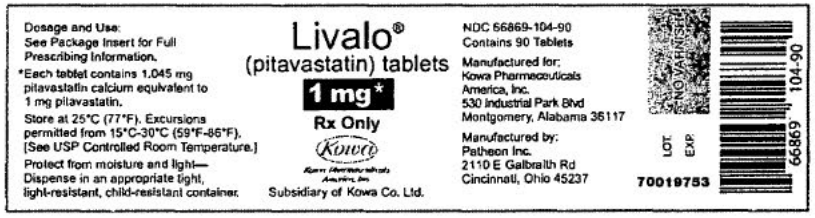
Manufactured for: Kowa Pharmaceuticals America, Inc, Montgomery, AL 36117
By: Patheon Inc., Cincinnati, OH, 45237
Rev: MM/YY

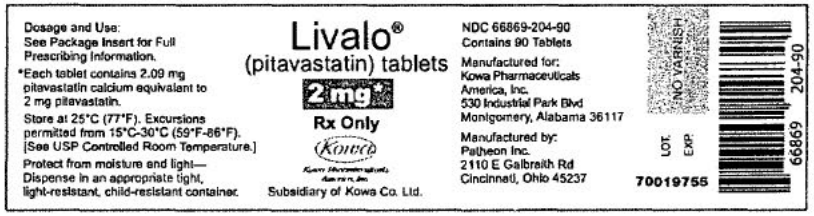

Livalo® (pitavastatin) tablets 2 mg*
Rx Only
Kowa Pharmaceuticals America, Inc.
Subsidiary of Kowa Co. Ltd.
Exp. Date: (MM/YYYY)
LOT:
*Each tablet contains:
Active ingredient: pitavastatin calcium 2.09 mg
equivalent to pitavastatin 2 mg.
Professional Sample - Not for Sale
70019767

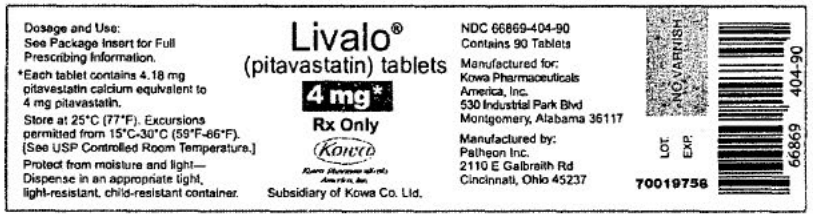

66869-204-07
NDC 66869-204-07
Livalo®
(pitavastatin) tablets
2mg
Rx Only
Contains 7 Tablets
Kowa Pharmaceuticals America, Inc.
Professional Sample -
Not for Sale
*Each tablet contains:
Active ingredient: pitavastatin calcium
2.09 mg equivalent to pitavastatin 2 mg.
Dosage and Use: See Package Insert for Full Prescribing Information.
Livalo® (pitavastatin) tablets 2mg
Rx Only
Manufactured for:
Kowa Pharmaceuticals America, Inc.
530 Industrial Park Blvd
Montgomery, Alabama 36117
Manufactured by: Patheon Inc.
2110 E Galbraith Rd
Cincinnati, Ohio 45237
Directions for use:
• To remove a single tablet, push the tablet through the foil seal from the front
• Take as directed by physician
• Ask your doctor or pharmacist if you have any questions about this medication
Store at room temperature, 25°C (77°F).
Excursions permitted to 15°C-30°C (59°F-86°F).
[See USP Controlled Room Temperature.]
KEEP OUT OF THE REACH OF CHILDREN.
NO VARNISH
Glue


Livalo® (pitavastatin) tablets 4 mg*
Rx Only
Kowa Pharmaceuticals America, Inc.
Subsidiary of Kowa Co. Ltd.
Exp. Date: (MM/YYYY)
LOT:
*Each tablet contains:
Active ingredient: pitavastatin calcium 4.18 mg
equivalent to pitavastatin 4 mg.
Professional Sample - Not for Sale
70019768


66869 404-07
NDC 66869-404-07
Livalo®
(pitavastatin) tablets
4 mg*
Rx Only
Contains 7 Tablets
Kowa
Professional Sample -
Not for Sale
*Each tablet contains:
Active ingredient: pitavastatin calcium
4.18 mg equivalent to pitavastatin 4 mg.
Dosage and Use: See Package Insert for Full Prescribing Information.
Livalo® (pitavastatin) tablets 4 mg*
Rx Only
Manufactured for:
Kowa Pharmaceuticals America, Inc.
530 Industrial Park Blvd
Montgomery, Alabama 36117
Manufactured by: Patheon Inc.
2110 E Galbraith Rd
Cincinnati, Ohio 45237
Directions for use:
• To remove a single tablet, push the tablet through the foil seal from the front
• Take as directed by physician
• Ask your doctor or pharmacist if you have any questions about this medication
Store at room temperature, 25°C (77°F). Excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature.]
KEEP OUT OF THE REACH OF CHILDREN.
Glue
LOT
EXP.
NO VARNISH


Dosage and Use:
See Package Insert for Full Prescribing Information.
*Each tablet contains 1.045 mg pitavastatin calcium equivalent to 1 mg pitavastatin.
Store at 25°C (77°F). Excursions permitted from 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature.]
Protect from moisture and light—Dispense in an appropriate tight, light-resistant, child-resistant container.
Livalo®
(pitavastatin) tablets
1 mg*
Rx Only
Subsidiary of Kowa Co. Ltd.
NDC 66869-104-90
Contains 90 Tablets
Manufactured for:
Kowa Pharmaceuticals America, Inc.
530 Industrial Park Blvd
Montgomery, Alabama 36117
Manufactured by:
Patheon Inc.
2110 E Galbraith Rd
Cincinnati, Ohio 45237
NO VARNISH
LOT
EXP
70019753
66869-104-90


Dosage and Use:
See Package Insert for Full Prescribing Information.
*Each tablet contains 2.09 mg pitavastatin calcium equivalent to 2 mg pitavastatin.
Store at 25°C (77°F). Excursions permitted from 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature.]
Protect from moisture and light—Dispense in an appropriate tight, light-resistant, child-resistant container.
Livalo®
(pitavastatin) tablets
2 mg*
Rx Only
Kowa
Subsidiary of Kowa Co. Ltd.
NDC 66869-204-90
Contains 90 Tablets
Manufactured for:
Kowa Pharmaceuticals America, Inc.
530 Industrial Park Blvd
Montgomery, Alabama 36117
Manufactured by:
Patheon Inc.
2110 E Galbraith Rd
Cincinnati, Ohio 45237
NO VARNISH
LOT
EXP
70019755
66869 204-90


Dosage and Use:
See Package Insert for Full Prescribing Information.
*Each tablet contains 4.18 mg pitavastatin calcium equivalent to 4 mg pitavastatin.
Store at 25°C (77°F). Excursions permitted from 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature.]
Protect from moisture and light—Dispense in an appropriate tight, light-resistant, child-resistant container.
Livalo®
(pitavastatin) tablets
4 mg*
Rx Only
Kowa
Subsidiary of Kowa Co. Ltd.
NDC 66869-404-90
Contains 90 Tablets
Manufactured for:
Kowa Pharmaceuticals America, Inc.
530 Industrial Park Blvd
Montgomery, Alabama 36117
Manufactured by:
Patheon Inc.
2110 E Galbraith Rd
Cincinnati, Ohio 45237
NO VARNISH
LOT
EXP.
70019756
66869 404-90

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
08/03/2009

Exhibit B

US005856336A

United States Patent [19]

Fujikawa et al.

[11] Patent Number: 5,856,336

[45] Date of Patent: Jan. 5, 1999

[54] QUINOLINE TYPE MEVALONOLACTONES

[75] Inventors: Yoshihiro Fujikawa; Mikio Suzuki; Hiroshi Iwasaki, all of Funabashi; Mitsuaki Sakashita; Masaki Kitahara, both of Shiraoka-machi, all of Japan

[73] Assignee: Nissan Chemical Industries Ltd., Tokyo, Japan

[21] Appl. No.: 883,398

[22] Filed: May 15, 1992

Related U.S. Application Data

[62] Division of Ser. No. 631,092, Dec. 19, 1990, which is a continuation of Ser. No. 233,752, Aug. 19, 1988.

[30] Foreign Application Priority Data

Aug. 20, 1987 [JP] Japan 62-207224
Jan. 26, 1988 [JP] Japan 63-15585
Aug. 3, 1988 [JP] Japan 63-193606

[51] Int. Cl.[6] A61K 31/47; C07D 215/12

[52] U.S. Cl. 514/311; 546/173

[58] Field of Search 546/173; 514/311

[56] References Cited

U.S. PATENT DOCUMENTS

5,753,675 5/1998 Wattanasin 514/311

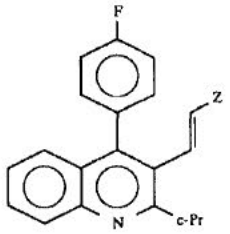
Primary Examiner—Laura L. Stockton

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

[57] ABSTRACT

A compound of the formula

[A]



Z=—CH(OH)—CH_2—CH(OH)—CH_2—COO.½Ca have HMG—CoA inhibiting effects, making them useful as inhibitors of cholesterol biosynthesis. The compound may be prepared as a pharmaceutical for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis.

2 Claims, No Drawings

QUINOLINE TYPE MEVALONOLACTONES

This is a division, of application Ser. No. 07/631,092, filed on Dec. 19, 1990, which is a continuation of 07/233,752, filed Aug. 19, 1988.

The present invention relates to novel mevalonolactones having a quinoline ring, processes for their production, pharmaceutical compositions containing them and their pharmaceutical uses particularly as anti-hyperlipidemic, hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

Some fermentation metabolic products such as compactine, CS-514, Mevinolin or semi-synthetic derivatives or fully synthetic derivatives thereof are known to be inhibitors against HMG-CoA reductase which is a rate limiting enzyme for cholesterol biosynthesis. (A. Endo J. Med Chem., 28(4) 401 (1985))

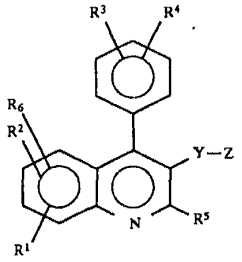
CS-514 and Mevinolin have been clinically proved to be potentially useful anti-hyperlipoproteinemic agents, and they are considered to be effective for curing or preventing diseases of coronary artery sclerosis or atherosclerosis. (IXth Int. Symp. Drugs Affect. Lipid Metab., 1986, p30, p31, p66)

However, with respect to fully synthetic derivatives, particularly hetero aromatic derivatives of inhibitors against HMG-CoA reductase, limited information is disclosed in the following literatures:

WPI ACC NO. 84-158675, 86-028274, 86-098816, 86-332070, 87-124519, 87-220987, 88-07781, 88-008460, 88-091798 and 88-112505.

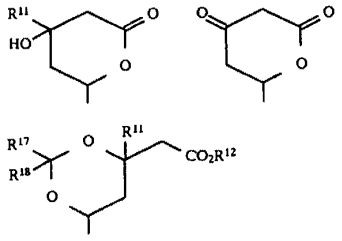
The present inventors have found that mevalonolactone derivatives having a quinoline ring, the corresponding dihydroxy carboxylic acids and salts and esters thereof have high inhibitory activities against cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme. The present invention has been accomplished on the basis of this discovery.

The novel mevalonolactone derivatives of the present invention are represented by the following formula I:

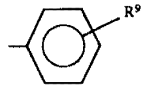


(I)

wherein R_1, R_2, R_3, R_4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $—O(CH_2)_lOR^{19}$ (wherein R^{19} is hydrogen or C_{1-3} alkyl, and l is 1, 2 or 3); or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together form —CH=CH—CH=CH—; or when located at the ortho position to each other, R^1 and R^2 together form $—OC(R^{15})(R^{16})O—$(wherein R^{15} and R^{16} are independently hydrogen or C_{1-3} alkyl); Y is $—CH_2—$, $—CH_2CH_2—$, —CH=CH—, $—CH_2—CH=CH—$ or $—CH=CH—CH_2—$; and Z is $-Q-CH_2WCH_2-CO_2R^{12}$,



(wherein Q is —C(O)—, $—C(OR^{13})_2—$ or —CH(OH)—; W is —C(O)—, $—C(OR^{13})_2—$ or $—C(R^{11})(OH)—$; R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen or R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, ½ calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine)); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $—(CH_2)_2—$ or $—(CH_2)_3—$; R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{2-3} alkenyl, C_{3-6} cycloalkyl,



(wherein R^9 is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-$(CH_2)_m$— (wherein m is 1, 2 or 3), $—(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$— (wherein n is 0, 1 or 2).

Various substituents in the formula I will be described in detail with reference to specific examples. However, it should be understood that the present invention is by no means restricted by such specific examples.

C_{1-6} alkyl for R^1, R^2, R^3, R^4, R^6 and R^9 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. C_{1-3} alkoxy for R^1, R^2, R^3, R^4 and R^6 includes, for example, methoxy, ethoxy, n-propoxy and i-propoxy.

C_{1-3} alkyl for R^{11} includes, for example, methyl, ethyl, n-propyl and i-propyl.

C_{1-3} alkyl for R^{13} includes, for example, methyl, ethyl, n-propyl and i-propyl.

Alkyl for R^{14} includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl and i-butyl.

M is a metal capable of forming a pharmaceutically acceptable salt, and it includes, for example, sodium and potassium.

CO_2M includes, for example, $—CO_2NH_4$ and $—CO_2H$. (primary to tertiary lower alkylamine such as trimethylamine).

C_{1-6} alkyl for R^5 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

C_{3-6} cycloalkyl for R^5 includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

C_{2-3} alkenyl for R^5 includes, for example, vinyl and i-propenyl.

Phenyl-$(CH_2)_m$- for R^5 includes, for example, benzyl, β-phenylethyl and γ-phenylpropyl.

Phenyl-$(CH_2)_nCH(CH_3)$— for R^5 includes, for example, α-phenylethyl and α-benzylethyl.

C_{1-3} alkyl for R^7 and R^8 includes, for example, methyl, ethyl, n-propyl and i-propyl.

Further, these compoundsmay have at least one or two asymmetric carbon atoms and may have at least two to four

optical isomers. The compounds of the formula I include all of these optical isomers and all of the mixtures thereof.

Among compounds having carboxylic acid moieties falling outside the definition of $—CO_2R^{12}$ of the carboxylic acid moiety of substituent Z of the compounds of the present invention, those which undergo physiological hydrolysis, after intake, to produce the corresponding carboxylic acids (compounds wherein the $—CO_2R^{12}$ moiety is $—CO_2H$) are equivalent to the compounds of the present invention.

Now, preferred substituents of the compounds of the present invention will be described.

In the following preferred, more preferred still further perferred and most preferred examples, the numerals for the positions of the substituents indicate the positions on the quinoline ring. For example, N' shown by e.g. 1' or 2' indicates the position of the substituent on the phenyl substituted at the 4-position of the quinoline ring (the carbon connected to the quinoline ring is designated as 1'). The meanings of the respective substituents are the same as the above-mentioned meanings.

Preferred substituents for R^1, R^2 and R^6 are hydrogen, fluoro, chloro, bromo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, dimethylamino, hydroxy, hydroxymethyl, hydroxyethyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, phenoxy and benzyloxy.

Further, when R^6 is hydrogen, it is preferred that R^1 and R^2 together form methylenedioxy.

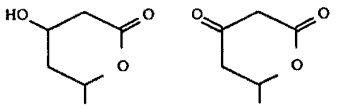
As preferred examples for R^3 and R^4, when R^4 is hydrogen, R^3 is hydrogen, 3'-fluoro, 3'-chloro, 3'-methyl, 4'-methyl, 4'-chloro and 4'-fluoro.

Other preferred combinations of R^3 and R^4 include 3'-methyl-4'-chloro, 3',5'-dichloro, 3',5'-difluoro, 3',5'-dimethyl and 3'-methyl-4'-fluoro.

Preferred examples for R^5 include primary and secondary C_{1-6} alkyl and C_{3-6} cycloalkyl.

Preferred examples for Y include $—CH_2—CH_2—$ and —CH=CH—.

Preferred examples for Z include



$—CH(OH)CH_2CH_2(OH)CH_2CO_2R^{12}$, $—CH(OH)CH_2C(O)CH_2CO_2R^{12}$ and $—CH(OH)CH_2C(OR^{13})_2CH_2CO_2R^{12}$.

Now, more preferred substituents of the compounds of the present invention will be described.

As more preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy, 8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-n-butyl and 7-dimethylamino.

When R^6 is hydrogen, R^1 and R^2 together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo, 6,7-difluoro, 6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo.

When R^1, R^2 and R^6 are not hydrogen, they together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo.

As more preferred examples for R^3 and R^4, when R^3 is hydrogen, R^4 is hydrogen, 4'-methyl, 4'-chloro or 4'-fluoro. When both R^3 and R^4 are not hydrogen, they together represent 3',5'-dimethyl or 3'-methyl-4'-fluoro.

As more preferred examples for R^5, the above-mentioned preferred examples of R^5 may be mentioned.

As preferred examples for Y, $—CH_2—CH_2—$ and (E)——CH=CH—may be mentioned. As more preferred examples for Z, the above preferred examples for Z may be mentioned.

Now, still further preferred substituents of the compounds of the present invention will be described. As examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl, 6-ethyl, 6-trifluoromethyl, 6-hydroxy, 6-methoxy, 6-chloro, 6-bromo, 6-n-butyl and 7-dimethylamino.

When only R^6 is hydrogen, R^1 and R^2 represent 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo, 6,8-dihromo, 6,7-difluoro and 6,8-difluoro.

As still further preferred examples for R^3 and R^4, when R^3 is hydrogen, R^4 is hydrogen, 4'-chloro or 4'-fluoro, or R^3 and R^4 together represent 3'-methyl-4'-fluoro.

Still further preferred examples for R^5 include ethyl, n-propyl, i-propyl and cyclopropyl.

Still further preferred examples for Y include (E)——CH=CH—.

As still further preferred examples for Z, the above-mentioned preferred example for Z may be mentioned.

Now, the most preferred substituents for the compounds of the present invention will be described.

As the most preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl or 6-chloro.

When only R^6 is hydrogen, R^1 and R^2 together represent, for example, 6,7-dimethoxy.

As the most preferred examples for R^3 and R^4, R^3 is hydrogen and R^4 is hydrogen, 4'-chloro or 4'-fluoro.

The most preferred examples for R^5 include i-propyl and cyclopropyl. The most preferred example for Y may be (E)——CH=CH—.

As the most preferred examples for Z, the above-mentioned preferred examples for Z may be mentioned.

Now, particularly preferred specific compounds of the present invention will be presented. The following compounds (a) to (z) are shown in the form of carboxylic acids. However, the present invention include not only the compounds in the form of carboxylic acids but also the corresponding lactones formed by the condensation of the carboxylic acids with hydroxy at the 5-position, and sodium salts and lower alkyl esters (such as methyl, ethyl, i-propyl and n-propyl esters) of the carboxylic acids, which can be physiologically hydrolyzed to the carboxylic acids.

(a) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(b) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(c) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(d) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(e) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(f) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(g) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(h) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(i) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(j) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(k) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(l) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(m) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(n) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(o) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(p) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(q) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(r) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(s) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(t) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(u) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(v) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

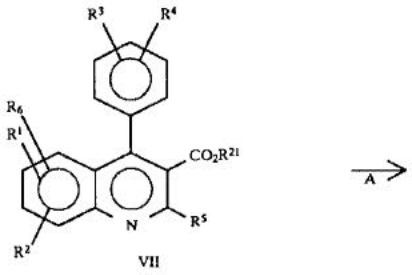
(w) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(x) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

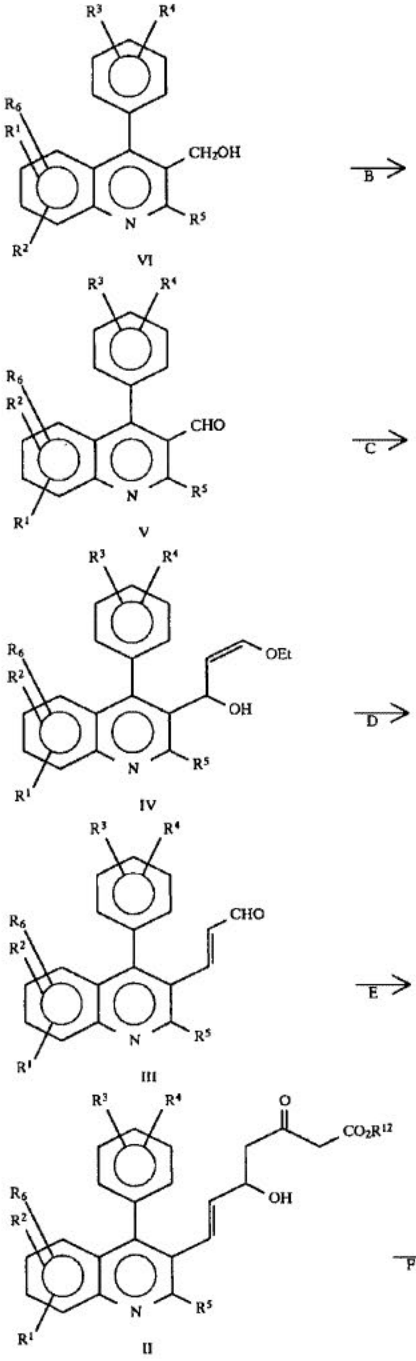
(y) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

(z) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

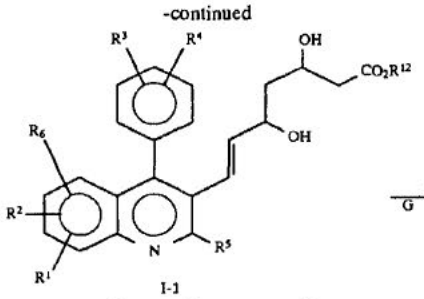
The mevalonolactones of the formula I can be prepared by the following reaction scheme. The enal III can also be prepared by processes K, L and M.



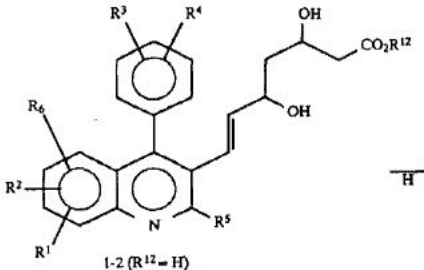
-continued



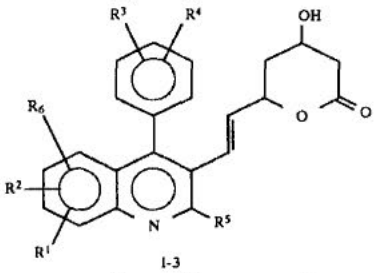
-continued



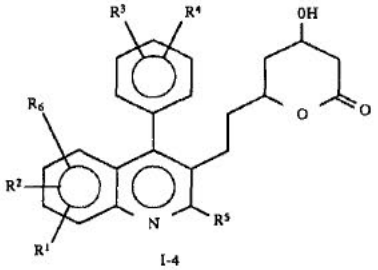
I-1



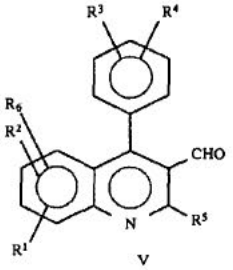
I-2 (R^{12} = H)
I-5 (R^{12} = Na)



I-3

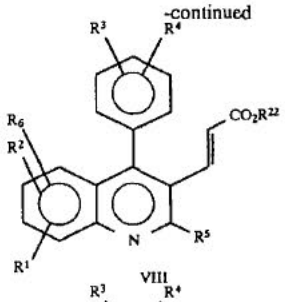


I-4

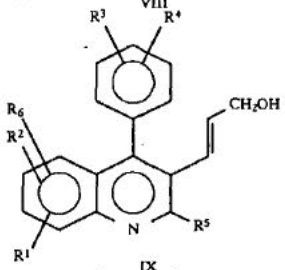


V

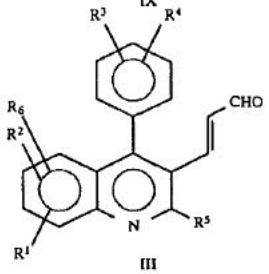
-continued



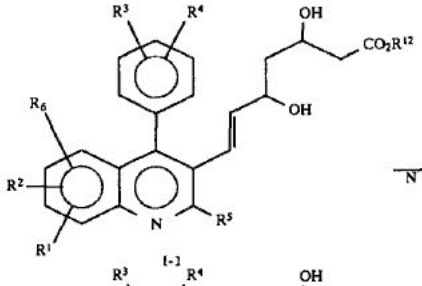
VIII



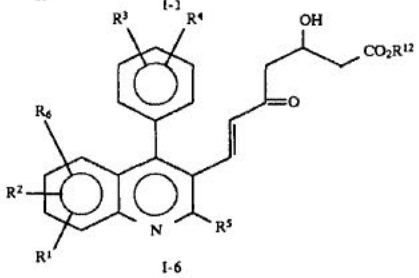
IX



III



I-2



I-6

In the above reaction scheme, R^1, R^2, R^3, R^4, R^5, R^6 and R^{12} are as defined above with respect to the formula I, and

R^{21} and R^{22} independently represent C_{1-4} lower alkyl such as methyl, ethyl, n-propyl, i-propyl or n-butyl.

Step A represents a reduction reaction of the ester to a primary alcohol. Such reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminium hydride, in a solvent such as tetrahydrofuran or toluene at a temperature of from −20° to 20° C., preferably from −10° to 10° C.

Step B represents an oxidation reaction of the primary alcohol to an aldehyde, which can be conducted by using various oxidizing agents. Preferably, the reaction can be conducted by using pyridinium chlorochromate in methylene chloride at a temperature of from 0° to 25 ° C., or by using oxalyl chloride, dimethyl sulfoxide and a tertiary amine such as triethylamine (Swern oxidation), or by using a sulfur trioxide pyridine complex.

Step C represents a synthesis of a 3-ethoxy-1-hydroxy-2-propene derivative, which can be prepared by reacting a compound V to lithium compound which has been preliminarily formed by treating cis-1-ethoxy-2-(tri-n-butylstannyl) ethylene with butyl lithium in tetrahydrofuran.

As the reaction temperature, it is preferred to employ a low temperature at a level of from −60° to −78° C.

Step D represents a synthesis of an enal by acidic hydrolysis. As the acid catalyst, it is preferred to employ p-toluene sulfonic acid, hydrochloric acid or sulfuric acid, and the reaction may be conducted in a solvent mixture of water and tetrahydrofuran or ethanol at a temperature of from 10° to 25° C. The 3-ethoxy-1-hydroxy-2-propene derivative obtained in Step C can be used in Step D without purification i.e. by simply removing tetra-n-butyl tin formed simultaneously.

Step E represents a double anion condensation reaction between the enal III and an acetoacetate. Such condensation reaction is preferably conducted by using sodium hydride and n-butyl lithium as the base in tetrahydrofuran at a temperature of from −80° to 0° C., preferably from −30° to −10° C.

Step F represents a reduction reaction of the carbonyl group, which can be conudcted by using a metal hydride, preferably sodium borohydride in ethanol at a temperature of from −10° to 25° C., preferably from −10° to 5° C.

Further, the reduction reaction may be conducted by using zinc borohydride in dry ethyl ether or dry tetrahydrofuran at a temperature of −100° to 25° C., preferably from −80° to −50° C.

Step G is a step for hydrolyzing the ester. The hydrolysis can be conducted by using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide, in a solvent mixture of water and methanol or ethanol at a temperature of from 10° to 25° C. The free acid hereby obtained may be converted to a salt with a suitable base.

Step H is a step for forming a mevalonolactone by the dehydration reaction of the free hydroxy acid I-2. The dehydration reaction can be conducted in benzene or toluene under reflux while removing the resulting water or by adding a suitable dehydrating agent such as molecular sieve.

Further, the dehydration reaction may be conducted in dry methylene chloride by using a lactone-forming agent such as carbodiimide, preferably a water soluble carbodiimide such as N-cyclohexyl-N'-[2'-(methylmorpholinium)ethyl] carbodiimide p-toluene sulfonate at a temperature of from 10° to 35 ° C., preferably from 20° to 25° C.

Step J represents a reaction for hydrogenating the double bond connecting the mevalonolactone moiety and the quinoline ring. This hydrogenation reaction can be conducted by using a catalytic amount of palladium-carbon or rhodium-carbon in a solvent such as methanol, ethanol, tetrahydrofuran or acetonitrile at a temperature of from 0° to 50° C., preferably from 10° to 25° C.

Step K represents a reaction for the synthesis of an α,β-unsaturated carboxylic acid ester, whereby a trans-form α,β-unsaturated carboxylic acid ester can be obtained by a so-called Horner-Wittig reaction by using an alkoxycarbonylmethyl phosphonate. The reaction is conducted by using sodium hydride or potassium t-butoxide as the base in dry tetrahydrofuran at a temperature of from −30° to 0° C., preferably from −20° to −15° C.

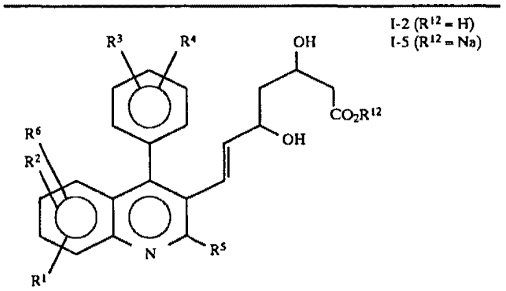
Step L represents a reduction reaction of the α,β-unsaturated carboxylic acid ester to an allyl alcohol. This reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminiumhydride, in a solvent such as dry tetrahydrofuran or toluene at a temperature of from −10° to 10° C., preferably from −10° to 0° C.

Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly active manganese dioxide, in a solvent such as tetrahydrofuran, acetone, ethyl ether or ethyl acetate at a temperatrue of from 0° to 100° C., preferably from 15° to 50° C.

Step N represents a reaction for the synthesis of an α,β-unsaturated ketone by the selective oxidation of the dihydroxy carboxylic acid ester. This reaction can be conducted by using activated manganese dioxide in a solvent such as ethyl ether, tetrahydrofuran, benzene or toluene at a temperature of from 20° to 80° C., preferably from 40° to 80° C.

In addition to the compounds disclosed in Examples given hereinafter, compounds of the formulas I-2 and I-5 given in Table 1 can be prepared by the process of the present invention. In Table 1, i- means iso, sec- means secondary and c- means cyclo. Likewise, Me means methyl, Et means ethyl, Pr means propyl, Bu means butyl, Pent means pentyl, Hex means hexyl and Ph means phenyl.

TABLE 1



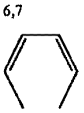
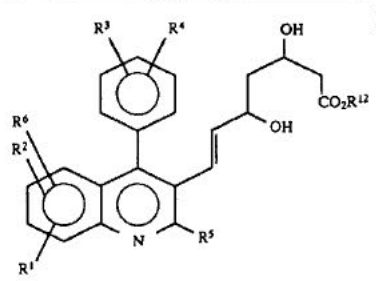
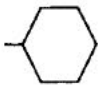
R^1	R^2	R^3	R^4	R^5	R^6
6-OMe	H	H	H	i-Pr	H
6-OMe	H	4-F	H	i-Pr	H
6-Br	H	4-F	H	i-Pr	H
6-Me	8-Me	4-F	H	i-Pr	H
7-OMe	8-OMe	4-F	H	i-Pr	H
6-Br	H	2-F	H	i-Pr	H
6,7		4-F	H	i-Pr	H

TABLE 1-continued



R^1	R^2	R^3	R^4	R^5	R^6
H	H	4-F	H		H
H	H	4-Ph	H	i-Pr	H
H	H	4-$PhCH_2$	H	i-Pr	H
6-Cl	H	4-F	H	c-Pr	H
6-Cl	H	4-F	H	sec-Bu	H
6-OCH_2Ph	H	4-F	H	i-Pr	H
H	H	4-F	H	i-Bu	H
H	H	4-F	H	c-Pent	H
6-Cl	H	4-F	H	c-Pent	H
6-Me_2N	H	4-F	H	i-Pr	H
6-Me	H	4-F	H	c-Pr	H
6-i-Pr	H	4-F	H	i-Pr	H
7-Me	H	4-F	H	c-Pr	H
6-OMe	H	4-F	H	c-Pr	H
6-Br	H	4-F	H	c-Pr	H
6-i-Pr	H	4-F	H	c-Pr	H
6-Cl	8-Cl	4-F	H	c-Pr	H
5-F	6-Br	4-F	H	i-Pr	8-Br
6-OMe	7-OMe	4-F	H	i-Pr	8-OMe
6-Me	7-Me	4-F	H	i-Pr	8-Me
6-Cl	7-Cl	4-F	H	i-Pr	8-Cl
H	H	4-F	H	c-Bu	H
H	H	4-F	H	c-Hex	H
6-OMe	7-OMe	H	H	i-Pr	H
6-OMe	7-OMe	4-Cl	H	i-Pr	H
6-OMe	7-OMe	H	H	c-Pr	H
6-OMe	7-OMe	4-Cl	H	c-Pr	H
6-OMe	7-OMe	4-F	H	c-Pr	H
6-Me	H	H	H	i-Pr	H
6-Me	H	4-Cl	H	i-Pr	H
6-Me	H	H	H	c-Pr	H
6-Me	H	4-Cl	H	c-Pr	H
6-Me	H	4-F	H	c-Pr	H
6-Cl	H	H	H	i-Pr	H
6-Cl	H	4-Cl	H	i-Pr	H
6-Cl	H	H	H	c-Pr	H
6-Cl	H	4-Cl	H	c-Pr	H
6-Cl	H	4-F	H	c-Pr	H
H	H	H	H	i-Pr	H
H	H	4-Cl	H	i-Pr	H
H	H	H	H	c-Pr	H
H	H	4-Cl	H	c-Pr	H
H	H	4-F	H	c-Pr	H

Further, pharmaceutically acceptable salts such as potassium salts or esters such as ethyl esters or methyl esters of these compounds can be prepared in the same manner.

The compounds of the present invention exhibit high inhibitory activities against the cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme, as shown by the test results given hereinafter, and thus are capable of suppressing or reducing the amount of cholesterol in blood as lipoprotein. Thus, the compounds of the present invention are useful as curing agents against hyperlipidemia, hyperlipoproteinemia and atheroscleosis.

They may be formulated into various suitable formulations depending upon the manner of the administration. The compounds of the present invention may be administered in the form of free acids or in the form of physiologically hydrolyzable and acceptable esters or lactones, or pharmaceutically acceptable salts.

The pharmaceutical composition of the present invention is preferably administered orally in the form of the compound of the present invention per se or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present invention with a suitable pharmaceutically acceptable carrier including a binder such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone or CMC-Ca, an excipient such as lactose, sugar, corn starch, calcium phosphate, sorbitol, glycine or crystal cellulose powder, a lubricant such as magnesium stearate, talk, polyethylene glycol or silica, and a disintegrator such as potato starch.

However, the pharmaceutical composition of the present invention is not limited to such oral administration and it is applicable for parenteral administration. For example, it may be administered in the form of e.g. a suppository formulated by using oily base material such as cacao butter, polyethylene glycol, lanolin or fatty acid triglyceride, a transdermal therapeutic base formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more materials selected from the group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and excipient such as lactose or corn starch, or a formulation for administration through mucous membranes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

Further, the compounds of the present invention may be combined with basic ion-exchange resins which are capable of binding bile acids and yet not being absorbed in gastrointestinal tract.

The daily dose of the compound of the formula I is from 0.05 to 500 mg, preferably from 0.5 to 50 mg for an adult. It is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the condition of illness of the patient.

The compounds of the formulas II to VII are novel, and they are important intermediates for the preparation of the compounds of the formula I. Accordingly, the present invention relates also to the compounds of the formulas II to VII and the processes for their production.

Now, the present invention will be described in further detail with reference to Test Examples for the pharmacological activities of the compounds of the present invention, their Preparation Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

PHARMACOLOGICAL TEST EXAMPLES

Test A: Inhibition of cholesterol biosynthesis from acetate in vitro

Enzyme solution was prepared from liver of male Wistar rat billialy cannulated and discharged bile for over 24 hours. Liver was cut out at mid-dark and microsome and supernatant fraction which was precipitable with 40–80% of saturation of ammonium sulfate (sup fraction) were prepared from liver homogenate according to the modified method of Knauss et. al.; Kuroda, M., et. al., Biochim. Biophys. Acta, 489, 119 (1977). For assay of cholesterol biosynthesis, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37° C. in 200 μl of the

reaction mixture containing ATP; 1 mM, Glutathione; 6 mM, Glucose-1-phosphate; 10 mM, NAD; 0.25 mM, NADP; 0.25 mM, CoA; 0.04 mM and 0.2 mM [2-^{14}C]sodium acetate (0.2 μCi) with 4 μl of test compound solution dissolved in water or dimethyl sulfoxide. To stop reaction and saponify, 1 ml of 15% EtOH-KOH was added to the reactions and heated at 75° C. for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and incorporated ^{14}C radioactivity was counted. Inhibitory activity of compounds was indicated with IC50.

Test B: Inhibition of cholesterol biosynthesis in culture cells

Hep G2 cells at over 5th passage were seeded to 12 well plates and incubated with Dulbecco's modified Eagle (DME) medium containing 10% of fetal bovine serum (FBS) at 37° C., 5% CO_2 until cells were confluent for about 7 days. Cells were exposed to the DME medium containing 5% of lipoprotein deficient serum (LpDS) prepared by ultracentrifugation method for over 24 hours. Medium was changed to 0.5 ml of fresh 5% LpDS containing DME before assay and 10 μl of test compound solution dissolved in water or DMSO were added. 0.2 μCi of [2-^{14}C]sodium acetate (20 μl) was added at O hr(B-1) or 4 hrs(B-2) after addition of compounds. After 4 hrs further incubation with [2-^{14}C] sodium acetate, medium was removed and cells were washed with phosphate buffered saline(PBS) chilled at 4° C. Cells were scraped with rubber policeman and collected to tubes with PBS and digested with 0.2 ml of 0.5N KOH at 37° C. Aliquot of digestion was used for protein analysis and remaining was saponified with 1 ml of 15% EtOH-KOH at 75° C. for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and ^{14}C radioactivity was counted. Counts were revised by cell protein and indicated with DPM/mg protein. Inhibitory activity of compounds was indicated with IC50.

Test C: Inhibition of cholesterol biosynthesis in vivo

Male Sprague-Dawley rats weighing about 150 g were fed normal Purina chow diet and water ad libitum, and exposed to 12 hours light/12 hours dark lighting pattern (2:00 PM–2:00 AM dark) prior to use for in vivo inhibition test of cholesterol biosynthesis. Animals were separated groups consisting of five rats as to be average mean body weight in each groups. Test compounds at dosage of 0.02–0.2 mg/kg body weight (0.4 ml/100 g body weight), were dissolved in water or suspended or in 0.5% methyl cellulose and orally administered at 2–3 hours before mid-dark (8:00 PM), while cholesterol biosynthesis reaches to maximum in rats. As control, rats were orally administered only water or vehicle. At 90 minutes after sample administration, rats were injected intraperitoneally with 10 μCi of [2-^{14}C]sodium acetate at volume of 0.2 ml per one. 2 Hours later, blood samples were obtained and serum were separated immediately. Total lipids were extracted according to the method of Folch et al. and saponified with EtOH-KOH. Nonsaponifiable lipids were extracted with petroleum ether and radio activity incorporated into nonsaponifiable lipids was counted.

Inhibitory activity was indicated as percent decrease of counts in testing groups (DPM/2 ml serum/2 hours) from that in control group.

With respect to the compounds of the present invention, the inhibitory activities against the cholesterol biosynthesis in which HMG-CoA reductase serves as a rate limiting enzyme, were measured by the above Test A and B. The results are shown in Tables, 2, 2-2, 3 and 3-2. Further, the results of the measurements by Test C are also presented.

TABLE 2

Inhibitory activities by Test A

Compound	I_{50} (molar concentration)
(Compounds of the present invention)	
I-13	1.25×10^{-7}
I-51	1.0×10^{-8}
I-52	7.1×10^{-8}
I-53	1.9×10^{-7}
(Reference compounds)	
Mevinolin	1.4×10^{-8}
CS-514	9.0×10^{-9}

In Table 2-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

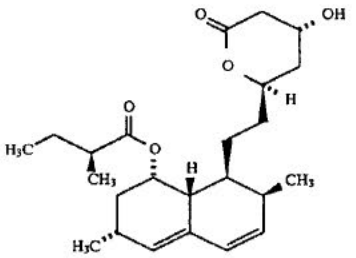
TABLE 2-2

Relative activities by Test A

Compound	Relative activities
(Compounds of the present invention)	
I-16	1.75
I-116	2.25
I-117	0.37
I-120	3.21
I-522	0.76

Structures of reference compounds:

(1) Mevinolin



(2) CS-514

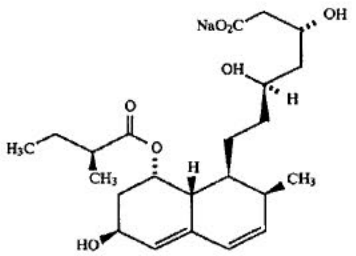


TABLE 3

Inhibitory activities by Test B-1

Compound	I_{50} (molar concentration)
(Compound of the present invention)	
I-51	1×10^{-7}
(Reference compound)	
CS-514	3.5×10^{-7}

In Table 3-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

TABLE 3-2

Relative activities by Test B-1

Compound	Relative activities
I-116	19.4
I-520	20.0
II-20	20.8

Results of the measurement of the inhibitory activities by Test C

The percent decrease of counts after the oral administration of 0.05 mg/kg of compound I-520 was 55% relative to the measured value of the control group. The percent decrease of counts after the oral administration of 10 mg/kg of CS-514 was 55% under the same condition. The compounds of the present invention exhibited activities superior to the reference compound such as CS-514 or Mevinolin in Test A, and exhibited activities superior to CS-514 in Tests B and C.

Test D: Acute toxicity

A 0.5% CMC suspension of a test compound was orally administered to ICR male mice (group of three mice). The acute toxicity was determined based on the mortality after seven days. With compound I-57, I-58, I-59, I-511, I-512, I-513, I-514, I-515, I-517 and I-523 of the present invention, the mortality was 0% even when they were orally administered in an amount of 1000 mg/kg.

Example 1

Ethyl (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoate (compound I-11) (prepared by steps of Example 1-a through Example I-q)

Example 1-a

Ethyl 4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinolin-3-yl-carboxylate (compound VII-1)

The synthesis was conducted in accordance with the method disclosed in J. Org. Chem., 2899 (1966).

6.45 g (0.03 mol) of 2-amino-4'-fluorobenzophenone, 5.53 g (0.035 mol) of ethyl isobutyrylacetate and 0.1 ml of conc. sulfuric acid were dissolved in 30 ml of glacial acetic acid, and the mixture was heated at 100° C. for about 10 hours. After confirming the substantial disappearance of 2-amino-4'-fluorobenzophenone by thin layer chromatography, the reaction solution was cooled to room temperature, and a mixture of 45 ml of conc. aqueous ammonia and 120 ml of water cooled with ice, was gradually added thereto. A separated oily substance was solidified when left to stand overnight in a refrigerator. This solid was recrystallized from a small amount of ethanol to obtain 6.47 g (55%) of white powder. Melting point: 68°–70.5° C.

Example 1-b

4-(4'-fluorophenyl)-3-hydroxymethyl-2-(1'-methylethyl)-quinoline (compound VI-1)

5.4 g (0.016 mol) of compound VII-1 was dissolved in dry toluene under a nitrogen atmosphere and cooled in ice bath to 0° C. To this solution, 40 ml of a 16 wt % diisobutylaluminium hydride-toluene solution was dropwise added, and the mixture was stirred at 0° C. for two hours. After confirming the complete disappearance of compound VII-1 by thin layer chromatography, a saturated ammonium chloride solution was added thereto at 0° C. to terminate the reaction. Ethyl ether was added to the reaction mixture, and the organic layer was separated. A gelled product was dissolved by an addition of an aqueous sodium hydroxide solution and extracted anew with ethyl ether. The ethyl ether extracts were put together, dried over anhydrous magnesium sulfate and filtered. The solvent was distilled off. The residual oil underwent crystallization when left to stand. It was recrystallized from ethyl acetate-n-hexane to obtain 3.3 g of white crystals. Yield: 70%. Melting point: 136°–137° C.

Example 1-c

4-(4'-fluorophenyl)-2-(1'-methyletbyl)-quinolin-3-yl-carboxyaldehyde (compound V-1)

2.0 g (9.3 mmol) of pyridinium chlorochromate and 0.4 g of anhydrous sodium acetate was suspended in 10 ml of dry dichloromethane. To this suspension, a solution obtained by dissolving 1 g (3.4 mmol) of compound VI-1 in 10 ml of dry dichloromethane, was immediately added at room temerature. The mixture was stirred for one hour. Then, 100 ml of ethyl ether was added thereto, and the mixture was throughly mixed. The reaction mixture was filtered under suction through a silica gel layer. The filtrate was dried under reduced pressure. The residue was dissolved in the isopropyl ether, and insoluble substances were filtered off. The filtrate was again dried under reduced pressure, and the residue was recrystallized from diisopropyl ether to obtain 0.7 g (Yield: 70%) of slightly yellow prism crystals. Melting point: 124°–126° C.

Example 1-d

3-(3'-ethoxy-1'-hydroxy-2'-propenyl)-4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinoline (compound IV-1)

1.13 g (3.13 mmol) of cis-1-ethoxy-2-(tri-n-butylstannyl) ethylene was dissolved in 8 ml of dry tetrahydrofuran, and the solution was cooled to −78° C. in a nitrogen stream. To this solution, 2 ml (3.2 mmol) of a 15 wt % n-butyllithium-n-hexane solution was dropwise added. The mixture was stirred for 45 minutes. Then, a solution prepared by dissolving 0.76 g (2.6 mmol) of compound V-1 in 10 ml of dry tetrahydrofuran was dropwise added thereto. The reaction mixture was stirred at −78° C. for two hours. Then, 2 ml of a saturated ammonium chloride solution was added thereto to terminate the reaction. The organic layer was extracted with diethyl ether, and the diethyl ether extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was separated with n-hexane and acetonitrile. The solvent was distilled off under reduced pressure from the acetonitrile layer, and an oily substance thereby obtained was purified by silica gel column chromatography (eluent: 2.5% methanol-chloroform) to obtain 0.91 g of the desired compound in a purified oily form.

H-MNR ($CDCl_3$) δ ppm: 1.1(t,3H,7Hz) 1.37(d,6H,J=7Hz) 3.7(m,1H); 3.7(q,2H,J=7Hz) 4.75(t,1H,7Hz) 5.7(m,1H) 5.95(m,1H) 7.05–8.2(m,8H)

Example 1-e

(E)-3-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]propenaldehyde (compound III-1)

0.91 g of compound IV-1 was dissolved in 20 ml of tetrahydrofuran, and 5 ml of water and 100 mg of p-toluenesulfonic acid were added thereto. The mixture was stirred at room temperature for 24 hours. The reaction solution was extracted with diethyl ether a few times. The extracts were washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent: chloroform) to obtain the desired product as white prism crystals. 0.4 g (50%). Melting point: 127°–128° C.

Example 1-f

Ethyl (E)-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-5-hydroxy-3-oxohepto-6-enoate (compound II-1)

50 mg of 60% sodium hydride was washed with dry petroleum ether and dried under a nitrogen stream, and then suspended in 5 ml of dry tetrahydrofuran. The suspension was cooled to −15° C. in a nitrogen atmosphere. Then, 120 mg (0.92 mmol) of ethyl acetoacetate was dropwise added thereto, and the mixture was stirred for 15 minutes. Then, 0.6 ml (0.92 mmol) of a 15 wt % n-butyllithium-n-hexane solution was dropwise added thereto, and the mixture was stirred for 30 minutes. Then, a solution prepared by dissolving 160 mg (0.5 mmol) of compound III-1 in dry tetrahydrofuran, was dropwise added thereto, and the mixture was stirred for one hour. To the reaction mixture, 1 ml of a saturated ammonium chloride aqueous solution was added at −15° C. Then, the mixture was extracted three times with diethyl ether. The diethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solution was evaporated to dryness under reduced pressure. The residue was recrystallized from diisopropyl ether to obtain 130 mg (yield: 59%) of white crystals. Melting point: 99°–101° C.

Example 1-g

Ethyl (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3 '-yl]-hept-6-enoate (compound I-11)

110 mg (0.245 mmol) of compound II-1 was dissolved in 5 ml of ethanol in a nitrogen atmosphere, and the solution was cooled 0° C. Then, 10 mg (0.263 mmol) of sodium borohydride was added, and the mixturer was stirred for one hour. Then, 1 ml of a 10% hydrochloric acid aqueous solution was added thereto, and the mixture was extracted three times with ethyl ether. The ethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solution was evaporated to dryness under reduced pressure. The residual oil was purified by silica gel column chromatography (eluent: 5% methanol-chloroform) to obtain the desired product as a pure colorless oily substance. 70 mg (Yield: 64%)

H-NMR ($CDCl_3$) δ ppm: 1.30(t,3H,J=8Hz) 139(d,6H,J=8Hz) 1.4–1.8(m,2H); 2.42(d,2H,J=7Hz) 3.0–3.8 (m,2H) 3.50(m,1H) 3.9–4.6(m,2H) 4.20(q,2H,J=8Hz) 5.35(m,1H) 6.59(m,1H) 7.10–8.18(m,8H)

Example 2

Sodium salt of (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3 '-yl]-hept-6-enoic acid (compound I-51)

60 mg (0.133 mmol) of compound I-11 was dissolved in 3 ml of ethanol. Then, 0.26 ml of a 0.5N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 5 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was freeze-dried to obtain 40 mg (67%) of hygroscopic white powder. Melting point: 207°–209° C. (decomposed).

Example 3

(E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid (compound I-21)

110 mg (0.244 mmol) of compound I-11 was dissolved in 10 ml of ethanol. Then, 0.79 ml of a 0.5N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 10 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was weakly acidified (pH 4) with a dilute hydrochloric aqueous solution and extracted three times with ethyl ether. The ethyl ether layers were put together and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure to obtain 90 mg of slightly yellow oily substance.

H-NMR ($CDCl_3$) δ ppm: 1.36(d,6H,J=7Hz) 2.4(m,2H) 3.5(m,1H) 3.45(m,1H); 3.8–4.6(m,2H) 5.40(dd,1H,J_1=19Hz,J_2=8Hz) 6.55 (d,1H,J=19Hz) 7.0–8.3(m,8H)

Example 4

(E)-6-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-ylethenyl]-4-hydroxy-3,4, 5,6-tetrahydro-2H-pyran-2-one (compound I-31)

90 mg of compound I-21 was dissolved in 10 ml of dry toluene, and the solution was refluxed under heating for 3 hours by means of a Dean Stark apparatus.

Toluene was distilled off under reduced pressure, and the residual solid was recrystallized from diisopropyl ether to obtain 40 mg of colorless prism crystals. Melting point: 182°–184 ° C.

By silica gel thin chromatography, the product gave two absorption spots close to each other attributable to the diastereomers. (Developping solvent: 3% methanol-chloroform)

These diasteromers were separated and isolated by silica gel thin layer chromatography. [Developping solvent: t-BuOMe/hexane/acetone=7/2/1 (v/v), Rf=0.6 and 0.7 (obtained weight ratio: 1/2)]

Rf=0.7: trans lactone

H-NMR ($CDCl_3$) δ ppm: 1.40(d,6H,J=7Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H); 4.20(m,1H) 5.15(m,1H) 5.37(dd, 1H,J_1=18Hz,J_2=7Hz) 6.68(d,1H, J=19Hz) 7.1–8.2(m,8H)

Rf=0.6: cis lactone

H-NMR ($CDCl_3$) δ ppm: 1.40(d,6H,J=7Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H); 4.20(m,1H) 4.65(m,1H) 5.40(dd, 1H,J_1=18Hz,J_2=7Hz) 6.66(m,1H) 7.0–8.2(m,8H)

Example 5

6-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-ylethynyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound I-41)

20 mg of a mixture of diastereomers of compound I-31 was dissolved in 5 ml of ethanol, and 10 mg of 5% palladium-carbon was added thereto. The mixture was stirred under a hydrogen atmosphere. After confirming the disappearance of the starting substance and the appearance of a new spot by thin layer chromatography, the palladium-carbon was filtered off, and ethanol was distilled off to obtain colorless oil.

This oil was purified by preparative thin layer chromatography to obtain 16 mg of the desired product as pure colorless oil.

MS(m/e): 408(M^++H), 407(M^+), 366, 292, 278

In the same manner as in Example 1-a, compounds VII-2 to VII-27 were prepared. The physical properties of these compounds are shown in Table 4. (In the Table, R^1, R^2, R^3, R^4, R^5 and R^{21} correspond to the substitients of compound VII.)

TABLE 4

(Compounds in this Table are compounds of the formula VII wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{21}	m.p. (°C.)
VII-2	H	H	4-F	H	CH_3	C_2H_5	121–122
VII-3	H	H	H	H	CH_3	C_2H_5	102–102.5
VII-4	H	H	H	H	i-Pr	C_2H_5	85–85.5
VII-5	6-Cl	H	H	H	CH_3	C_2H_5	100.5–101.5
VII-6	6-Cl	H	H	H	i-Pr	C_2H_5	105.5–106.5
VII-7	H	H	2-F	H	i-Pr	C_2H_5	101.0–102.0
VII-8	7-Me	H	H	H	i-Pr	C_2H_5	oil
VII-9	H	H	4-Cl	H	i-Pr	C_2H_5	134.0–136.5
VII-10	H	H	4-OMe	H	i-Pr	C_2H_5	88.0–89.0
VII-11	H	H	4-Me	H	i-Pr	C_2H_5	108.5–109.5
VII-12	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	101.0–103.0
VII-13	H	H	4-CF_3	H	i-Pr	C_2H_5	117.5–119.0
VII-14	H	H	3-Me	4-F	i-Pr	C_2H_5	oil
VII-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
VII-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	96.0–98.0
VII-17	H	H	4-F	H	C_2H_5	CH_3	139.0–139.5
VII-18	H	H	4-F	H	n-Pr	C_2H_5	oil
VII-19	6-Cl	H	4-F	H	i-Pr	C_2H_5	94.5–95.5
VII-20	H	H	4-F	H	c-Pr	CH_3	113.5–116.5
VII-21	H	H	4-OPh	H	i-Pr	C_2H_5	oil
VII-22	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	96.0–98.0
VII-23	6-Cl	H	H	H	Ph	C_2H_5	118.8–119.5
VII-24	6-Cl	H	H	H	c-Pr	CH_3	97.0–98.5
VII-25	H	H	4-F	H	sec-Bu	CH_3	oil
VII-26	6-Me	H	4-F	H	i-Pr	C_2H_5	109.0–111.0
VII-27	6-OMe	7-OMe	4-F	H	c-Pr	CH_3	153.0–153.5

VII-8

H-NMR (in $CDCl_3$) δ ppm: 0.92 (t,3H,J=7Hz), 1.41 (d,6H,J=6Hz); 2.47 (s,3H), 3.27 (Heptaplet,1H,J=6Hz) 3.96 (q,2H,J=7Hz), 7.0–7.8(m, 8H)

VII-14

H-NMR (in $CDCl_3$) δ ppm: 1.01 (t,3H,J=7Hz), 1.42 (d,6H,J=6Hz); 2.38 (s,3H,J=3Hz), 3.25(Heptaplet, 1H,J=6Hz) 4.04 (q,2H,J=7Hz), 6.9 –8.1(m,7Hz)

VII-15

H-NMR(in $CDCl_3$) δ ppm: 0.97(t,3H,J=7Hz), 1.43 (d,6H, J=6Hz); 2.29 (s,6H) 3.25 (Heptaplet, 1H,J=6Hz) 4.00 (q,2H, J=7Hz), 6.8–8.0(m,7H)

VII-18

H-NMR (in $CDCl_3$) δ ppm: 0.98 (t,3H,J=7Hz), 1.02 (t,3H,J=7Hz); 1.6–2.3(m,2H), 2.8–3.1(m,2H) 4.03 (q,2H,J=7Hz), 6.9–8.1(m,8H)

VII 21

H-NMR (in $CDCl_3$) δ ppm: 1.03 (t,3H,J=7Hz), 1.41 (d,6H,J=6Hz); 3.25(Heptapet,1H,J=6Hz), 4.05(q,2H,J=7Hz), 6.8–8.1(m, 13H)

VII-25

H-NMR (in $CDCl_3$) δ ppm: 0.97 (d,6H,J=6Hz), 2.0–2.6 (m,1H); 2.85 (d,2H,J=7Hz), 3.51(s,3H), 6.8–8.1 (m,8H)

In the same manner as in Example 1-b, compounds VI-2 to VI-27 were prepared. (In Table 5, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in compound VI.)

TABLE 5

(Compounds in this Table are compounds of the formula VI wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
VI-2	H	H	p-F	H	CH_3	—
VI-3	H	H	H	H	CH_3	149–151
VI-4	H	H	H	H	i-Pr	130–130.5
VI-5	6-Cl	H	H	H	CH_3	139–141
VI-6	6-Cl	H	H	H	i-Pr	168–169
VI-7	H	H	2-F	H	i-Pr	140.5–142.0
VI-8	7-Me	H	H	H	i-Pr	155.0–157.0
VI-9	H	H	4-Cl	H	i-Pr	192.0–195.0
VI-10	H	H	4-OMe	H	i-Pr	186.0–188.5
VI-11	H	H	4-Me	H	i-Pr	161.0–164.0
VI-12	6-Cl	H	2-Cl	H	i-Pr	122.0–124.0
VI-13	H	H	4-CF_3	H	i-Pr	183.0–186.0
VI-14	H	H	3-Me	4-F	i-Pr	161.0–162.5
VI-15	H	H	3-Me	5-Me	i-Pr	137.0–138.0
VI-16	6-Me	7-OMe	4-F	H	i-Pr	164.0–165.0
VI-17	H	H	4-F	H	C_2H_5	141.5–143.5
VI-18	H	H	4-F	H	n-Pr	146.5–148.5
VI-19	6-Cl	H	4-F	H	i-Pr	171.0–172.0
VI-20	H	H	4-F	H	c-Pr	120–126
VI-21	H	H	4-OPh	H	i-Pr	153.0–154.0
VI-22	6-Cl	8-Cl	4-F	H	i-Pr	98.5–103
VI-23	6-Cl	H	H	H	Ph	171.5–172.5
VI-24	6-Cl	H	H	H	c-Pr	84.0–86.0
VI-25	H	H	4-F	H	sec-Bu	119.0–121.0
VI-26	6-Me	H	4-F	H	i-Pr	160.0–161.5
VI-27	6-OMe	7-OMe	4-F	H	c-Pr	162.0–163.0

In the same manner as in Example 1-c, compounds V-2 to V-27 were prepared. (In Table 6, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound of V.)

TABLE 6

(Compounds in this Table are compounds of the formula V wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
V-2	H	H	p-F	H	CH_3	125–128
V-3	H	H	H	H	CH_3	143–146
V-4	H	H	H	H	i-Pr	92–93
V-5	6-Cl	H	H	H	CH_3	220–222
V-6	6-Cl	H	H	H	i-Pr	140–140.5
V-7	H	H	2-F	H	i-Pr	121.5–124.0
V-8	7-Me	H	H	H	i-Pr	105.1–109.2
V-9	H	H	4-Cl	H	i-Pr	147.0–147.8
V-10	H	H	4-OMe	H	i-Pr	135.6–136.8
V-11	H	H	4-Me	H	i-Pr	119.4–120.4
V-12	6-Cl	H	2-Cl	H	i-Pr	105.8–106.9
V-13	H	H	4-CF_3	H	i-Pr	163.7–164.2
V-14	H	H	3-Me	4-F	i-Pr	161.1–108.1
V-15	H	H	3-Me	5-Me	i-Pr	120.8–122.3
V-16	6-OMe	7-OMe	4-F	H	i-Pr	164.4–165.2
V-17	H	H	4-F	H	C_2H_5	143.1–144.2
V-18	H	H	4-F	H	n-Pr	150.2–155.3
V-19	6-Cl	H	4-F	H	i-Pr	164.5–165.3
V-20	H	H	4-F	H	c-Pr	150.1–151.6
V-21	H	H	4-OPh	H	i-Pr	106.9–107.7
V-22	6-Cl	8-Cl	4-F	H	i-Pr	135.0–135.7
V-23	6-Cl	H	H	H	Ph	174.8–175.3
V-24	6-Cl	H	H	H	c-Pr	157.5–158.0
V-25	H	H	4-F	H	sec-Bu	125.0–126.5
V-26	6-Me	H	4-F	H	i-Pr	155.0–157.0
V-27	6-OMe	7-OMe	4-F	H	c-Pr	200.0–200.5

In the same manner as in Example 1-d, compounds IV-2 to IV-6 were prepared. (In Table 7, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound IV.)

TABLE 7

(Compounds in this Table are compounds of the formula IV wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
IV-2	H	H	4-F	H	CH_3	177–179
IV-3	H	H	H	H	CH_3	—
IV-4	H	H	H	H	i-Pr	—
IV-5	6-Cl	H	H	H	CH_3	—
IV-6	6-Cl	H	H	H	i-Pr	—

In the same manner as in Example 1-e, compounds III-2 to III-27 were prepared. (In Table 8, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound III.)

TABLE 8

(Compounds in this Table are compounds of the formula III wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
III-2	H	H	4-F	H	CH_3	194–196
III-3	H	H	H	H	CH_3	170–171.5
III-4	H	H	H	H	i-Pr	107–108.5
III-5	6-Cl	H	H	H	CH_3	192–194
III-6	6-Cl	H	H	H	i-Pr	125.5–127
III-7	H	H	2-F	H	i-Pr	80.1–80.2
III-8	7-Me	H	H	H	i-Pr	121.1–122.3
III-9	H	H	4-Cl	H	i-Pr	148.0–149.1
III-10	H	H	4-OMe	H	i-Pr	137.4–140.1
III-11	H	H	4-Me	H	i-Pr	111.6–113.1
III-12	6-Cl	H	2-Cl	H	i-Pr	83.8–84.5
III-13	H	H	4-CF_3	H	i-Pr	126.2–128.8
III-14	H	H	3-Me	4-F	i-Pr	124.8–126.4
III-15	H	H	3-Me	5-Me	i-Pr	117.6–120.3
III-16	6-OMe	7-OMe	4-F	H	i-Pr	147.8–150.9
III-17	H	H	4-F	H	C_2H_5	124.3–128.5
III-18	H	H	4-F	H	n-Pr	117.8–121.5
III-19	6-Cl	H	4-F	H	i-Pr	135.2–135.9
III-20	H	H	4-F	H	c-Pr	141.3–144.1
III-21	H	H	4-OPh	H	i-Pr	oil
III-22	6-Cl	8-Cl	4-F	H	i-Pr	117–122
III-23	6-Cl	H	H	H	Ph	142.8–144.3
III-24	6-Cl	H	H	H	c-Pr	161.0–161.5
III-25	H	H	4-F	H	sec-Bu	78.0–81.0
III-26	6-Me	H	4-F	H	i-Pr	137.0–137.5
III-27	6-OMe	7-OMe	4-F	H	c-Pr	189.5–191.0

III-22

H-NMR(in $CDCl_3$) δ ppm: 1.40(d6H,J=7Hz), 3.44 (Heptaplet,1H,J=7Hz); 5.93(dd,1H,J=8Hz,J=16Hz), 6.8–8.1 (m,14H) 9.34(d,1H,J=8Hz)

In the same manner as in Example 1-f, compounds II-2 to II-27 were prepared. (In Table 9, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound II.)

TABLE 9

(Compounds in this Table are compounds of the formula of II wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
II-2	H	H	p-F	H	CH_3	C_2H_5	oil
II-3	H	H	H	H	CH_3	C_2H_5	105–106
II-4	H	H	H	H	i-Pr	C_2H_5	88.5–90.5
II-5	6-Cl	H	H	H	CH_3	C_2H_5	77–82
II-6	6-Cl	H	H	H	i-Pr	C_2H_5	96–98
II-7	H	H	2-F	H	i-Pr	C_2H_5	oil
II-8	7-Me	H	H	H	i-Pr	C_2H_5	68.5–74.0
II-9	H	H	4-Cl	H	i-Pr	C_2H_5	91.0–94.0

TABLE 9-continued

(Compounds in this Table are compounds of the formula of II wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
II-10	H	H	4-OMe	H	i-Pr	C_2H_5	78.0–78.5
II-11	H	H	4-OMe	H	i-Pr	C_2H_5	75.0–78.0
II-12	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	oil
II-13	H	H	4-CF_3	H	i-Pr	C_2H_5	78.0–83.0
II-14	H	H	3-Me	4-F	i-Pr	C_2H_5	66.0–71.0
II-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
II-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	83.0–90.0
II-17	H	H	4-F	H	C_2H_5	C_2H_5	94.0–97.0
II-18	H	H	4-F	H	n-Pr	C_2H_5	oil
II-19	6-Cl	H	4-F	H	i-Pr	C_2H_5	111.0–113.5
II-20	H	H	4-F	H	c-Pr	C_2H_5	91.0–93.0
II-21	H	H	4-OPh	H	i-Pr	C_2H_5	121.0–125.0
II-22	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	oil
II-23	6-Cl	H	H	H	Ph	C_2H_5	oil
II-24	6-Cl	H	H	H	c-Pr	C_2H_5	69.0–71.0
II-25	H	H	4-F	H	sec-Bu	C_2H_5	oil
II-26	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
II-27	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	oil

II-7

H-NMR(in $CDCl_3$) δ ppm: 1.21(t,3H,J=7Hz), 1.32(d,6H, J=6Hz); 2.2–2.4(m,2H), 2.5–2.7(m,1H) 3.28(s,1H), 3.34 (Heptaplet, 1H,J=6Hz) 4.08(q,2H,J=7Hz), 4.3–4.6(m,1H) 5.28(dd,1H,J=6Hz,J=15Hz), 6.53(dd,1H,J=1.5Hz,J=15Hz), 6.9–8.0(m,8H)

II-12

H-NMR(in $CDCl_3$) δ ppm: 1.25(t,3H,J=7Hz), 1.33(d,6H, J=6Hz); 2.2–2.4(m,2H), 2.5–2.8(m,1H); 3.32(s,2H), 3.38 (Heptaplet, 1H, J=6Hz); 4.13(q,2H,J=7Hz), 4.2–4.6(m,1H); 5.34(dd,1H,J=6Hz, J=15Hz), 6.53(dd,1H,J=1.5Hz,J=15Hz), 7.0–8.0(m,7H)

II-15

H-NMR (in $CDCl_3$) δ ppm: 1.23(t,3H,J=7Hz), 1.35(d,6H, J=6Hz); 2.2–2.4(m,2H), 2.31(s,6H); 2.6–2.8(m,1H), 3.32(s, 2H); 3.35(Heptaplet,1H,J=6Hz), 4.12(q,2H,J=7Hz); 4.3–4.7 (m,1H), 5.30(dd,1H,J=6Hz,J=16Hz); 6.51(dd,1H,J=1Hz,J= 16Hz), 6.7–8.0(m,7H)

II-18

H-NMR (in $CDCl_3$) δ ppm: 1.00 (t,3H,J=7Hz), 1.26(t, 3H,J=7Hz); 1.6–2.3(m,2H), 2.42 (d, 2H,J=6Hz); 2.6–3.2(m, 3H), 3.35(s,2H) 4.11(q,2H,J=7Hz), 4.3–4.7(m,1H) 5.27(dd, 1H,J=6Hz,J=16Hz) 6.46(dd,1H,J=1.5Hz,J=16Hz), 6.9–8.0 (m,8H)

II22

H-NMR(in $CDCl_3$) δ ppm: 1.26(t,3H,J=7Hz), 1.33(d,6H, J=6Hz); 2.43(d,2H,J=6Hz), 2.6–2.9(m,1H) 3.36(s, 2H), 3.44 (Heptaplet,1H,J=6Hz) 4.13(q,2H,J=7Hz), 4.3–4.7(m,1H) 5.30(dd,1H,J=6Hz,J=16Hz), 6.53(dd,1H,J=1.5Hz,J=16Hz), 7.0–7.6(m,6H)

II-23

H-NMR(in $CDCl_3$) δ ppm: 1.23(t,3H,J=7Hz), 2.21(d,2H, J=6Hz); 2.4–2.6(m,1H), 3.25(s,2H) 4.09(q,2H,J=7Hz), 4.1–4.4(m,1H) 5.08(dd,1H,J=6Hz,J=16Hz), 6.26(dd,1H,J= 1.5Hz,J=16Hz), 7.0–8.0 (m,13H)

II25

H-NMR(in $CDCl_3$) δ ppm: 0.96(d,6H,J=6Hz), 1.26(t,3H, J=7Hz), 1.8–2.4(m,1H), 2.43 (d,2H,J=6Hz), 2.6–2.9(m,1H), 2.88(d,2H,J=7Hz), 3.36(s,2H), 4.14(q,2H,J=7Hz), 4.3–4.7 (m,1H), 5.0–5.5(m,1H), 6.3–6.7(m,1H), 6.9–8.1(m,3H)

II-26

H-NMR(in $CDCl_3$) δ ppm: 1.25(t,3H, J=7Hz), 1.32(d,6H, J=6Hz), 2.32(s,3H), 2.39(d,2H, J=7Hz), 2.6–3.1(m,1H),

3.36(s,2H), 3.41(Heptaplet,1H,J=6Hz), 4.11(q,2H,J=7Hz), 4.3–4.7(m,1H), 5.0–5.5(m,1H), 6.3–6.7(m,1H), 6.8–7.9(m, 7H)

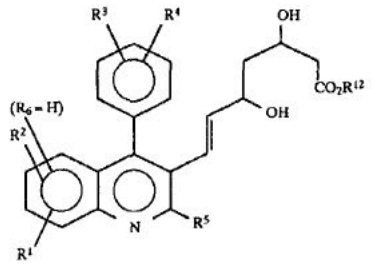
II-27

H-NMR (in $CDCl_3$) δ ppm: 0.8–1.5(m,4H), 1.26(t,3H,J=7Hz), 2.0–2.9(m,4H), 3.42(s,2H), 3.71(s,3H), 4.00(s,3H), 4.20(q,2H,J=7Hz), 4.4–4.8(m,1H), 5.3–5.8(m,1H), 6.4–6.9 (m,1H), 6.58(s,1H), 7.0–7.5(m,5H)

In the same manner as in Example 1-g, compounds I-12 to I-127 were prepared.

TABLE 10

I-1



Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.) Mass spectrum
I-12	H	H	4-F	H	CH_3	C_2H_5	oil
						M/e	423, 292 264, 249
I-13	H	H	H	H	CH_3	C_2H_5	92–105
I-14	H	H	H	H	i-Pr	C_2H_5	97–100
I-15	6-Cl	H	H	H	CH_3	C_2H_5	oil
I-16	6-Cl	H	H	H	i-Pr	C_2H_5	oil
I-17	H	H	2-F	H	i-Pr	C_2H_5	oil
I-18	7-Me	H	H	H	i-Pr	C_2H_5	oil
I-19	H	H	4-Cl	H	i-Pr	C_2H_5	98–104
I-110	H	H	4-OMe	H	i-Pr	C_2H_5	94–98
I-111	H	H	4-Me	H	i-Pr	C_2H_5	79–85
I-112	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	oil
I-113	H	H	4-CF_3	H	i-Pr	C_2H_5	117–128
I-114	H	H	3-Me	4-F	i-Pr	C_2H_5	85–92
I-115	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
I-116	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	gum
I-117	H	H	4-F	H	C_2H_5	C_2H_5	oil
I-118	H	H	4-F	H	n-Pr	C_2H_5	oil
I-119	6-Cl	H	4-F	H	i-Pr	C_2H_5	79–82
I-120	H	H	4-F	H	c-Pr	C_2H_5	100–104
I-121	H	H	4-OPh	H	i-Pr	C_2H_5	oil
I-222	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	133–143
I-123	6-Cl	H	H	H	Ph	C_2H_5	gum
I-124	6-Cl	H	H	H	c-Pr	C_2H_5	oil
I-125	H	H	4-F	H	sec-Bu	C_2H_5	oil
I-126	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
I-127	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	gum

I-17

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.40(d,6H, J=6Hz); 1.4–1.7(m,2H), 2.3–2.5(m,2H) 2.9–3.2(m,1H), 3.49(Heptaplet,1H,J=6Hz) 3.5–3.8(m,1H), 3.9–4.5(m,2H) 4.20(q,2H,J=7Hz), 5.2–5.7(m,1H) 6.5–6.9(m,1H), 7.0–8.2 (m,8H)

I-18

H-NMR (in $CDCl_3$) δ ppm: 1.0–1.4(m,2H), 1.31(t,3H,J=7Hz); 1.39(d,6H,J=6Hz), 2.3–2.5(m,2H) 2.52(s,3H), 3.1–3.4 (m,1H) 3.48(Heptaplet,1H,J6Hz),3.5–3.8(m,1H) 3.8–4.1(m,1H), 4.20(q,2H,J=7Hz) 4.2–4.5(m,1H), 5.2–5.6 (m,1H) 6.4–6.8(m,1H), 7.0–8.0(m,8H)

I-19

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.38(d,6H, J=6Hz); 1.4–1.8(m,2H), 2.3–2.5(m,2H) 3.2–3.4(m,1H), 3.49(Heptaplet,1H,J=6Hz) 3.6–3.8(m,1H), 3.9–4.2(m,1H) 4.20(q,2H,J=7Hz), 4.3–4.5(m,1H) 5.2–5.5(m,1H), 6.5–6.8 (m,1H) 7.0–8.2(m,8H)

I-110

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.40(d,6H, J=6Hz); 1.5–1.6(m,2H), 2.3–2.5(m,2H) 2.8–3.0(m,1H), 3.4–3.6(m,1H) 3.52(Heptaplet,1H,J=6Hz), 3.88(s,3H) 3.9–4.1(m,1H), 4.20(q,2H,J=7Hz) 4.3–4.5(m,1H), 5.3–5.5 (m,1H) 6.5–6.7(m,1H), 6.9–8.1(m,8H)

H-NMR (in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.3–1.5(m, 2H); 1.39(d,6H,J=6Hz), 2.3–2.5(m,2H) 2.43(s,3H), 2.8–3.0 (m,1H) 3.50(Heptaplet,1H,J=6Hz), 3.5–3.7(m,1H) 3.9–4.2 (m,1H), 4.19(q,2H,J=7Hz) 4.2–4.5(m,1H), 5.2–5.6(m,1H) 6.4–6.8(m,1H), 6.9–8.2(m,8H)

I-112

H-NMR (in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.3–1.6(m, 2H); 1.37(d,6H,J=6Hz), 2.3–2.5(m,2H) 2.9–3.2(m,1H), 3.47 (Heptaplet,1H ,J=6Hz) 3.5–3.8(m,1H), 3.9–4.1(m,1H) 4.19 (q,2H,J=7Hz), 4.2–4.5(m,1H) 5.3–5.7(m,1H), 6.5–6.8(m, 1H) 7.1–8.1(m,7H)

I-113

H-NMR(in $CDCl_3$) δ ppm: 1.0–1.3(m,2H), 1.30(t,3H,J=7Hz); 1.40(d,6H,J=6Hz), 2.3–2.4(m,2H) 3.3–3.5(m,1H), 3.49 (Heptaplet,1H,J=6Hz) 3.6–3.7(m,1H), 3.9–4.1(m,1H) 4.18(q,2H,J=7Hz), 4.2–4.5(m,1H) 5.1–5.5(m,1H), 6.5–6.8 (m,1H) 7.2–8.2(m,8H)

I-114

H-NMR (in $CDCl_3$) δ ppm: 1.2–1.4(m,2H), 1.30(t,3H,J=7Hz); 1.39(d,6H,J=6Hz), 2.32(bs,3H) 2.3–2.5(m,2H), 3.0–3.3(m,1H) 3.50(Heptaplet,1H,J=6Hz), 3.6–3.8(m,1H) 3.8–4.1(m,1H), 4.20(q,2H,J=7Hz) 4.3–4.6(m,1H), 5.2–5.6 (m,1H) 6.5–6.8(m,1H), 7.0–8.2(m,7H)

I-115

H-NMR (in $CDCl_3$) δ ppm: 1.1–1.4(m,2H), 1.30(t,3H,J=7Hz); 1.40(d,6H,J=6Hz), 2.2–2.5(m,2H) 2.35(s,6H), 2.7–3.1(m,1H) 3.51(Heptaplet, 1H,J=6Hz), 3.6–3.7(m,1H) 3.8–4.1(m,1H), 4.20 (q,2H,J=7Hz) 4.2–4.6(m,1H), 5.2–5.6 (m,1H) 6.4–6.8(m,1H), 6.8–8.2(m,7H)

I-116

H-NMR (in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.37(d,6H, J=6Hz); 1.5–1.8(m,2H), 2.3–2.5(m,2H) 2.9–3.2(m,1H), 3.46 (Heptaplet,1H,J=6Hz) 3.6–3:8(m,1H), 3.75(s,3H) 3.9–4.1(m,1H), 4.07(s,3H) 4.20(q,2H,J=7Hz), 4.2–4.5(m, 1H) 5.1–5.5(m,1H), 6.4–6.8(m,2H) 7.1–7.5(m,5H)

I-117

H-NMR(in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.37(t,3H, J=7Hz); 1.4–1.7 (m,2H), 2.2–2.6(m,2H) 2.8–3.2(m,3H), 3.6–3.9(m,1H) 3.9–4.7(m,4H), 5.2–5.7(m,1H) 6.3–6.7(m, 1H) 7.0–8.2(m,8H)

I-118

H-NMR (in $CDCl_3$) δ ppm: 1.01(t,3H,J=7Hz), 1.27(t,3H, J=7Hz); 1.4–2.1(m,4H), 2.3–2.6(m,2H); 2.8–3.3(m,3H), 3.6–3.3(m,1H); 3.9–4.1(m,1H), 4.18(q,2H,J=7Hz); 4.2–4.5 (m,1H), 5.2–5.6(m,1H); 6.4–6.7(m,1H), 7.0–8.1(m,8H);

I-119

H-NMR (in $CDCl_3$) δ ppm: 1.2–1.5(m,2H), 1.31(t,3H,J=7Hz); 1.37(d,6H,J=7Hz), 2.3–2.6(m,2H); 3.0–3.4(m,1H), 3.49(Heptaplet,1H,J=6Hz); 3.6–3.8(m,1H), 3.8–4.2(m,1H); 4.20(q,2H,J=7Hz), 4.3–4.5(m,1H); 5.2–5.6(m,1H), 6.4–6.8 (m,1H); 7.0–8.1(m,7H);

I-120

H-NMR (in CDCl3) δ ppm: 0.8–1.8(m,6H), 1.30(t,3H,J=7Hz); 2.1–2.6(m,3H), 2.9–3.3(m,1H); 3.4–3.7(m,1H), 3.8–4.6(m,2H); 4.20(q,2H,J=7Hz), 5.4–5.8(m,1H); 6.4–6.3 (m,1H), 6.8–8.0(m,8H);

I-121

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.39(d,6H, J=6Hz); 1.4–1.9(m,2H), 2.3–2.5(m,2H); 2.7–3.2(m,1H),

3.51(Heptaplet,1H,J=6Hz); 3.6–3.8(m,1H), 3.9–4.2(m,1H); 4.19(q,2H,J=7Hz), 4.3–4.6(m,1H); 5.2–5.6(m,1H), 6.4–6.8 (m,1H); 6.9–8.2(m,13H);

I-122

H-MNR (in $CDCl_3$) δ ppm: 1.1–1.8(m,2H), 1.31(t,3H,J=7Hz); 1.41(d,6H,J=6Hz), 2.3–2.5(m,2H); 2.9–3.4(m,1H), 3.50(Heptaplet,1H,J=6Hz); 3.6–3.8(m,1H), 3.9–4.5(m,2H); 4.20(q,2H,J=7Hz), 5.2–5.6(m,1H); 6.4–6.8 (m,1H), 7.1–7.3 (m,5H); 7.72(d,1H,J=6Hz);

I-123

H-NMR (in $CDCl_3$) δ ppm: 0.8–1.5(m,2H), 1.29(t,3H,J=7Hz); 2.2–2.4(m,2H), 2.6–2.9(m,1H); 3.2–3.6(m,1H), 3.7–4.3(m,2H); 4.17(q,2H,J=7Hz), 5.0–5.4(m,1H); 6.1–6.5 (m,1H), 7.0–8.2(m,13H);

I-124

H-NMR (in $CDCl_3$) δ ppm: 0.8–1.8(m,6H), 1.29(t,3H,J=7Hz), 2.2–2.6(m,3H), 2.8–3.2(m,1H), 3.3–3.7(m,1H), 3.9–4.5(m,2H), 4.19(q,2H,J=7Hz), 5.4–5.8(m,1H), 6.5–6.8 (m,1H), 7.1–8.0(m,8H),

I-125

NMR (in $CDCl_3$) δ ppm: 0.94(d,6H,J=6Hz), 1.0–1.7(m, 3H), 1.27(t,3H,J=7Hz), 1.9–2.5(m,3H), 2.90(d,2H,J=7Hz), 3.3–4.4(m,3H), 4.12(q,2H,J=7Hz), 5.0–5.5(m,1H), 6.2–6.7 (m,1H), 6.9–8.0(m,8H),

I-126

H-NMR (in $CDCl_3$) δ ppm: 1.0–1.6(m,3H), 1.21(t,3H,J=7Hz), 1.34(d,6H,J=6Hz), 2.34(s,3H), 2.37(d,2H,J=7Hz), 2.9–3.7(m,2H), 3.8–4.5(m,2H), 4.15(q,2H,J=7Hz), 5.0–5.5 (m,1H), 6.3–6.7(m,1H), 6.9–8.0(m,7H),

I-127

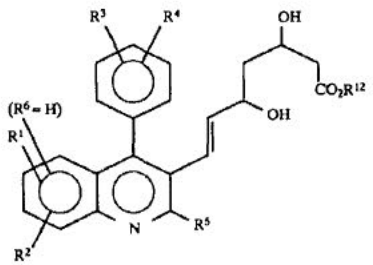
H-NMR (in $CDCl_3$) δ ppm: 0.8–1.9(m,8H), 1.29(t,3H,J=7Hz),

2.1–2.6(m,3H), 2.8–3.2(m,1H), 3.72(s,3H), 4.02(s,3H), 4.19(q,2H,J=7Hz), 4.3–4.6(m,1H), 5.4–5.8(m,1H), 6.4–6.8 (m,1H), 6.56(s,1H), 7.0–7.4(m,5H)

In the same manner as in Exmple 2, compounds I-52 to I-527 were prepared.

TABLE 11

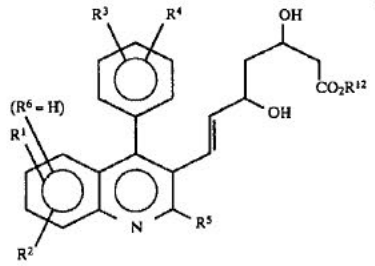
I-5 (R^{12} = Na)



Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
I-52	H	H	4-F	H	CH_3	Na	138–142 (decomposed)
I-53	H	H	H	H	CH_3	Na	130–132 (decomposed)
I-54	H	H	H	H	i-Pr	Na	196–197 (decomposed)
I-55	6-Cl	H	H	H	CH_3	Na	211–215 (decomposed)
I-56	6-Cl	H	H	H	i-Pr	Na	195–198 (decomposed)
I-57	H	H	2-F	H	i-Pr	Na	193–201 (decomposed)
I-58	7-Me	H	H	H	i-Pr	Na	170–175 (decomposed)
I-59	H	H	4-Cl	H	i-Pr	Na	193–202 (decomposed)
I-510	H	H	4-OMe	H	i-Pr	Na	178–193 (decomposed)
I-511	H	H	4-Me	H	i-Pr	Na	187–200 (decomposed)
I-512	6-Cl	H	2-Cl	H	i-Pr	Na	203–209 (decomposed)
I-513	H	H	4-CF_3	H	i-Pr	Na	200–212 (decomposed)
I-514	H	H	3-Me	4-F	i-Pr	Na	195–200 (decomposed)
I-515	H	H	3-Me	5-Me	i-Pr	Na	192–197 (decomposed)
I-516	6-OMe	7-OMe	4-F	H	i-Pr	Na	239–245 (decomposed)
I-517	H	H	4-F	H	C_2H_5	Na	230–237 (decomposed)
I-518	H	H	4-F	H	n-Pr	Na	193–200 (decomposed)

TABLE 11-continued

I-5 (R^{12} = Na)



Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
I-519	6-Cl	H	4-F	H	i-Pr	Na	193–198 (decomposed)
I-520	H	H	4-F	H	c-Pr	Na	197–199 (decomposed)
I-521	H	H	4-OPh	H	i-Pr	Na	180–189 (decomposed)
I-522	6-Cl	8-Cl	4-F	H	i-Pr	Na	183–187 (decomposed)
I-523	6-Cl	H	H	H	Ph	Na	190–196 (decomposed)
I-524	6-Cl	H	H	H	c-Pr	Na	204–210 (decomposed)
I-525	H	H	4-F	H	sec-Bu	Na	—
I-526	6-Me	H	4-F	H	i-Pr	Na	204–208 (decomposed)
I-527	6-OMe	7-OMe	4-F	H	c-Pr	Na	234–238 (decomposed)

I-57

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.2(m,2H), 1.37(d, 6H,J=7Hz); 1.6–2.1(m,2H), 3.48(Heptaplet,1H,J=6Hz); 3.7–4.3(m,4H), 5.3–5.6(m,1H); 6.4–6.7(m,1H), 7.1–8.1(m, 8H);

I-58

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.2(m,2H), 1.31(d, 6H,J=7Hz); 1.7–2.2(m,2H), 2.50(s,3H); 3.3–4.5(m,5H), 5.2–5.6(m,1H); 6.3–6.6(m,1H), 7.1–7.9(m,8H);

I-59

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.48(Heptaplet,1H,J=7Hz); 3.5–4.6(m,4H), 5.2–5.6(m,2H); 6.3–6.6(m,1H), 7.1–8.1(m, 8H);

I-510

H-NMR (in DMSO-d^6) δ ppm: 1.0–1.3(m,2H), 1.32(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.0–3.8(m,4H); 3.86(s,3H), 4.0–4.3(m,1H); 5.3–5.6(m,1H), 6.3–6.6(m,1H); 6.9–8.1(m, 8H);

I-511

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.7–2.1(m,2H), 2.41(s,3H); 3.2–4.3(m,5H), 5.3–5.6(m,1H); 6.3–6.6(m,1H), 7.0–8.3(m,8H);

I-512

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.1–3.8(m,3H); 3.48(Heptaplet, 1H,J=7Hz),3.9–4.2(m,1H); 5.3–5.7(m,1H), 6.3–6.7(m,1H); 7.0–8.1(m,7H);

I-513

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.3(m,2H), 1.34(d,6H, J=7Hz); 1.6–2.2(m,2H), 2.7–3.9(m,3H); 3.49(Heptaplet,1H, J=7Hz), 3.9–4.3(m,1H); 5.2–5.6(m,1H), 6.3–6.7(m,1H); 7.1–8.1(m,8H);

I-514

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2 H), 1.35(d, 6H,J=7Hz); 1.7–2.1(m,2H), 2.30(d,3H,J=2Hz); 3.0–3.8(m, 3H), 3.51(Heptaplet,1H,J=7Hz); 3.9–4.3(m,1H), 5.3–5.6(m, 1H); 6.3–6.6(m,1H), 6.9–8.1(m,7H);

II-515

H-NMR (in DMSO-d^6) δ ppm: 1.0–1.2(m,2H), 1.35(d, 6H,J=7Hz); 1.6–2.2(m,2H), 2.35(s,6H); 3.0–3.8(m,3H), 3.51(Heptaplet,1H,J=7Hz); 4.0–4.3(m,1H), 5.3–5.6(m,1H); 6.3–6.6(m,1H), 6.8–8.0(m,7H);

I-516

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.31(d, 6H,J=7Hz); 1.7–2.0(m,2H), 3.2–3.7(m,4H); 3.62(s,3H), 3.9–4.2(m,1H); 3.94(s,3H), 5.1–5.5(m,1H); 6.2–6.6(m,1H), 7.0–7.5(m,6H);

I-517

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.5(m,2H), 1.34(t,3H, J=7Hz); 1.6–2.2(m,2H), 2.7–3.4(m,4H); 3.6–4.3(m,2H), 5.2–5.7(m,1H); 6.1–6.6(m,1H), 6.9–8.1(m,8H);

I-518

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.3(m,2H), 1.01(t,3H, J=7Hz); 1.6–2.1(m,4H), 2.7–3.8(m,5H); 3.9–4.3(m,1H), 5.2–5.7(m,1H); 6.3–6.6(m,1H), 7.1–8.1(m,8H);

I-519

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.6–2.2(m,2H), 2.9–3.9(m,3H); 3.49(Heptaplet, 1H,J=7Hz), 4.0–4.3(m,1H); 5.3–5.6(m,1H), 6.3–6.6(m,1H); 7.2–8.1(m,7H);

I-520

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.5(m,6H), 1.7–2.2 (m,2H); 2.3–2.7(m,1H), 3.0–3.9(m,3H); 4.0–4.3(m,1H), 5.5–5.8(m,1H); 6.4–6.7(m,1H), 7.2–8.0(m,8H);

I-521

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.5(m,2H), 1.36(d, 6H,J=7Hz); 1.7–2.3(m,2H), 3.0–3.9(m,3H); 3.50(Heptaplet,

1H,J=6Hz), 4.0–4.3(m,1H); 5.2–5.6(m,1H) 6.4–6.7(m,1H); 7.0–8.1 (m,13H);

I-522

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.3(m,2H), 1.37(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.1–3.9(m,3H); 3.51(Heptaplet, 1H,J=7Hz),4.0–4.3(m,1H); 5.3–5.7(m,1H), 6.3–6.7(m,1H); 7.1–8.0(m,6H);

I-523

H-NMR (in DMSO-d6) δ ppm: 0.8–1.4(m,2H), 1.6–2.1 (m,2H); 2.9–3.7(m,3H), 3.7–4.1(m,1H); 5.1–5.4(m,1H), 6.1–6.4(m,1H); 7.1–8.2(m,13H);

I-524

H-NMR (in DMSO-d6) δ ppm: 0.8–1.5(m,5H), 1.6–2.2 (m,2H); 2.3–2.7(m,2H), 3.0–3.8(m,3H); 3.9–4.3(m,1H), 5.4–5.8(m,1H); 6.3–6.6(m,1H), 7.0–8.0(m,8H);

I-525

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.6(m,2H) 0.96(d,6H, J=6Hz); 1.7–2.6(m,3H), 2.89(d,2H,J=7Hz); 3.0–3.8(m,3H), 3.9–4.2(m,1H); 5.2–5.6(m,1H), 6.2–6.6(m,1H); 7.1–8.1(m, 8H);

I-526

H-NMR (in DMSO-d^6) δ ppm: 1.30(d,6H,J=7Hz), 1.7–2.0(m,2H), 2.34(s,3H), 2.4–2.6(m,1H), 3.0–3.3(m,2H), 3.3–3.8(m,3H); 3.9–4.2(m,1H), 5.2–5.6(m,1H); 6.3–6.6(m, 1H), 7.0–8.0(m,7H);

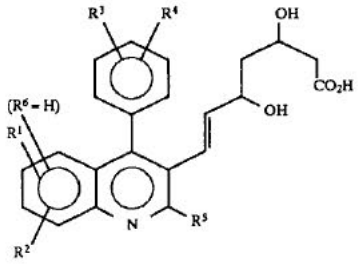
I-527

H-NMR (in DMSO-d^6) δ ppm: 0.7–1.5(m,5H), 1.8–2.2 (m,2H), 2.2–2.6(m,2H), 3.1–3.3(m,2H), 3.59(s,3H), 3.9–4.2 (m,2H), 3.91(s,3H), 5.4–5.7(m,1H), 6.3–6.6(m,1H), 6.52(s, 1H), 7.0–7.4(m,5H);

In the same manner as in Example 3, compounds I-22 to I-26 can be prepared.

TABLE 12

I-2

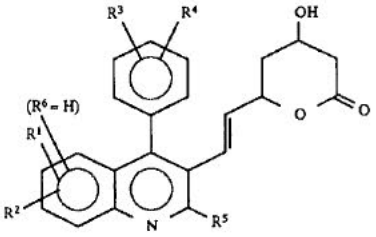


Compound	R¹	R²	R³	R⁴	R⁵
I-22	H	H	4-F	H	CH_3
I-23	H	H	H	H	CH_3
I-24	H	H	H	H	i-Pr
I-25	6-Cl	H	H	H	CH_3
I-26	6-Cl	H	H	H	i-Pr

In the same manner as in Example 4, compounds I-32 to I-36 can be prepared.

TABLE 13

I-3



Compound	R¹	R²	R³	R⁴	R⁵
I-32	H	H	4-F	H	CH_3
I-33	H	H	H	H	CH_3
I-34	H	H	H	H	i-Pr
I-35	6-Cl	H	H	H	CH_3
I-36	6-Cl	H	H	H	i-Pr

FORMULATION EXAMPLE 1

Tablets	
Compound I-51	1.0 g
Lactose	5.0 g
Crystal cellulose powder	8.0 g
Corn starch	3.0 g
Hydroxypropyl cellulose	1.0 g
CMC-Ca	1.5 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 2

Capsules	
Compound I-51	1.0 g
Lactose	3.5 g
Crystal cellulose powder	10.0 g
Magnesium stearate	0.5
Total	15.0 g

The above components were mix ed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

Soft capsules	
Compound I-51	1.00 g
PEG (polyethylene glycol) 400	3.89 g
Saturated fatty acid triglyceride	15.00 g
Peppermint oil	0.01 g
Polysorbate 80	0.10 g
Total	20.00 g

The above components were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment	
Compound I-51	1.0 g (10.0 g)
Liquid paraffin	10.0 g (10.0 g)
Cetanol	20.0 g (20.0 g)
White vaseline	68.4 g (59.4 g)
Ethylparaben	0.1 g (0.1 g)
L-menthol	0.5 g (0.5 g)
Total	100.0 g

The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository	
Compound I-51	1.0 g
Witepsol H15*	46.9 g
Witepsol W35*	52.0 g
Polysorbate 80	0.1 g
Total	100.0 g

*Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into suppository containers, followed by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active component.

FORMULATION EXAMPLE 6

Injection formulation	
Compound I-51	1 mg
Distilled water for injection formulation	5 ml

The formulation is prepared by dissolving the compound in the distilled water whenever it is required.

FORMULATION EXAMPLE 7

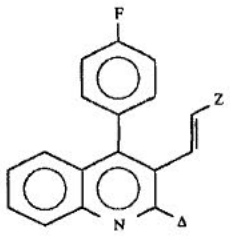
Granules	
Compound I-51	1.0 g
Lactose	6.0 g
Crystal cellulose powder	6.5 g
Corn starch	5.0 g
Hydroxypropyl cellulose	1.0 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

We claim:

1. A compound of the formula,

[A]



Z=—CH(OH)—CH_2—CH(OH)—CH_2—COO.½Ca.

2. A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in claim 1.

* * * * *

Exhibit C

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 22850 | ISTMT | DATE PRINTED 09/09/2009

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTA
1940 DUKE STREET
ALEXANDRIA VA 22314

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,856,336	$880.00	$0.00	06/13/02	07/883,398	01/05/99	05/15/92	04	NO	49-168-0-DIV

PTOL-439 (Rev. 09/2006)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 22850 | ISTMT | DATE PRINTED 09/09/2009

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTA
1940 DUKE STREET
ALEXANDRIA VA 22314

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,856,336	**$2,300.00**	**$0.00**	**06/09/06**	**07/883,398**	**01/05/99**	**05/15/92**	**08**	**NO**	**49-168-0-DIV**

PTOL-439 (Rev. 09/2006)

Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 07233752 **Filing Dt:** 08/19/1988 **Patent #:** NONE **Issue Dt:**
PCT #: NONE **Publication #:** NONE **Pub Dt:**
Inventors: YOSHIHIRO FUJIKAWA, MIKIO SUZUKI, HIROSHI IWASAKI, MITSUAKI SAKASHITA, MASAKI KITAHARA
Title: QUINOLINE TYPE MEVALONOLACTONES

Assignment: 1

Reel/Frame: 004960 / 0609 **Received:** **Recorded:** 10/18/1988 **Mailed:** NONE **Pages:** 2
Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.
Assignors: FUJIKAWA, YOSHIHIRO **Exec Dt:** 10/03/1988
SUZUKI, MIKIO **Exec Dt:** 10/03/1988
IWASAKI, HIROSHI **Exec Dt:** 10/03/1988
SAKASHITA, MITSUAKI **Exec Dt:** 10/03/1988
KITAHARA, MASAKI **Exec Dt:** 10/03/1988
Assignee: NISSAN CHEMICAL INDUSTRIES LTD., 7-1, 3-CHOME, KANDA-NISHIKI-CHO, CHIYODA-KU, TOKYO, JAPAN
Correspondent: OBLON, FISHER, SPIVAK,
MC CLELLAND & MAIER
1755 S. JEFF. DAVIS HWY.
CRYSTAL SQ. FIVE-STE. 400
ARLINGTON, VA 22202

Search Results as of: 09/15/2009 02:42 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: October 18, 2008 v.2.0.1

Assignment Of Application

WHEREAS, I (WE) Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita and Masaki Kitahara

of Nissan Chemical Industries Ltd. Chuo Kenkyusho, 722-1, Tsuboi-cho, Funabashi-shi, Chiba-ken, Japan, - ditto -, - ditto -, Nissan Chemical Industries Ltd. Seibutsukagaku Kenkyusho, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama-ken, Japan and - ditto -

, respectively,

have invented certain new and useful improvements in: QUINOLINE TYPE MEVALONOLACTONES,

for which an application for Letters Patent was executed on October 3, 1988, and

WHEREAS, Nissan Chemical Industries Ltd.

(hereinafter referred to as "ASSIGNEE") having a place of business at: 7-1, 3-chome, Kanda-Nishiki-cho, Chiyoda-ku, Tokyo, Japan,

is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent that may be granted therefor in the United States and its territorial possessions and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I (WE), by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

I (WE) hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my (our) entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me (us) had this Assignment and sale not been made.

Further, I (WE) agree that I (WE) will communicate to said ASSIGNEE or its (his) representatives any facts known to me (us) respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

The undersigned hereby grant(s) the firm of Oblon, Fisher, Spivak, McClelland & Maier, P.C. of 1755 S. Jefferson Davis Highway, Crystal Square, Arlington, Virginia 22202 the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

EXECUTED AT: JAPAN

Date: October 3, 1988 — Yoshihiro Fujikawa
(Signature of Inventor) Yoshihiro Fujikawa

Date: October 3, 1988 — Mikio Suzuki
(Signature of Inventor) Mikio Suzuki

Date: October 3, 1988 — Hiroshi Iwasaki
(Signature of Inventor) Hiroshi Iwasaki

Date: October 3, 1988 — Mitsuaki Sakashita
(Signature of Inventor) Mitsuaki Sakashita

Date: October 3, 1988 — Masaki Kitahara
(Signature of Inventor) Masaki Kitahara

Date: RECORDED PATENT & TRADEMARK OFFICE OCT 18 88 — (Signature of Inventor)

Date: — (Signature of Inventor)

Date: COMMISSIONER OF PATENTS AND TRADEMARKS OFFICE — (Signature of Inventor)

OBLON, FISHER, SPIVAK, McCLELLAND & MAIER, P.C.
PATENT & TRADEMARK ATTORNEYS
CRYSTAL SQUARE FIVE – SUITE 400
1755 S. JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202

Exhibit E

KOWA

RESEARCH INSTITUTE, INC.

September 25, 2009

Ms. Mary Till
Office of Patent Legal Administration
U.S. Patent and Trademark Office
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Re: Application for Extension of Patent Term
For U.S. Patent No. 5,856,336

Dear Ms. Till:

Kowa Research Institute, Inc., ("KRI") assumed ownership of IND 60,492 (relating to Livalo® – film-coated tablets of pitavastatin calcium) from Sankyo Pharma Inc. in 2005, and has remained the marketing applicant in IND 60,492 before the Food and Drug Administration from the time of assuming ownership of IND 60,492 to the present. In 2008, KRI filed NDA 022363 as the authorized agent of Kowa Company, Ltd. ("KCL"). KCL, through KRI, remained the marketing applicant in NDA 022363 before the Food and Drug Administration through approval. KCL and KRI authorize Nissan Chemical Industries, Ltd. ("Nissan"), to rely on the activities of the marketing applicants before the Food and Drug Administration in regard to IND 60,492 and NDA 022363 in connection with Nissan's application for extension of the term of U.S. Patent No. 5,856,336.

With best regards,

Very truly yours,

Ross S. Laderman, MPH
Senior Director, Regulatory Affairs

430 Davis Drive, Suite 200, Morrisville, North Carolina 27560 Telephone: 919.433.1600 Fax: 919.433.1620

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

DEC - 8 2009

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 5,856,336 was filed on September 30,2009, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, LIVALO® (pitavastatin calcium), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Stephen G. Baxter
Jacob A. Doughty
Oblon Spivak McClelland Maier & Neustadt LLP
1940 Duke Street
Alexandria, VA 22314

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 3 2010

Re: LIVALO
Docket No. FDA-2010-E-0042

The Honorable David J. Kappos
Undersecretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the application for patent term extension for U.S. Patent No. 5,856,336 filed by Nissan Chemical Industries, Ltd., under 35 U.S.C. § 156. The product claimed by the patent is LIVALO (pitavastatin calcium), which was assigned new drug application (NDA) No. 22-363.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1).

The NDA was approved on August 3, 2009, the submission of the patent term extension application on September 30, 2009, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Stephen G. Baxter
Oblon, Spivak, McClelland, Maier & Neustadt, PC
Customer 22850
1940 Duke Street
Alexandria, VA 22314

OBLON
SPIVAK

ATTORNEYS AT LAW

STEPHEN G. BAXTER
(703) 413-3000
SBAXTER@OBLON.COM

JACOB A. DOUGHTY
(703) 413-3000
JDOUGHTY@OBLON.COM

DOCKET NO.: 342163US68SD

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 07/883,398
Patentees: Yoshihiro FUJIKAWA et al
Filing Date: May 15, 1992
Patent No: 5,856,336
Issued: January 5, 1999
For: QUINOLINE TYPE MEVALONOLACTONES
Group Art Unit: 1613
Examiner: STOCKTON, L.L.

SIR:

Attached hereto for filing are the following papers:

SUPPLEMENT TO APPLICATION FOR EXTENSION OF PATENT TERM
WITH ATTACHED EXHIBIT F

Credit card payment is being made online (if electronically filed), or is attached hereto (if paper filed), in the amount of $0.00 to cover any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R. 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. **15-0030**. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, L.L.P.

Stephen G. Baxter
Registration No. 32,884

Jacob A. Doughty
Registration No. 46,671

Customer Number
22850
(703) 413-3000 (phone)
(703) 413-2220 (fax)
(OSMMN 10/09)

DOCKET NO: 342163US68SD

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE PATENT OF	:
YOSHIHIRO FUJIKAWA ET AL	: GROUP ART UNIT: 1613
SERIAL NO: 07/883,398	: EXAMINER: STOCKTON, L. L.
FILED: MAY 15, 1992	: PATENT NO. 5,856,336
FOR: QUINOLINE TYPE MEVALONOLACTONES	: ISSUED: JANUARY 5, 1999

SUPPLEMENT TO APPLICATION FOR EXTENSION OF PATENT TERM

MAIL STOP: PATENT TERM EXTENSION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Nissan Chemical Industries, Ltd. ("Nissan"), filed an Application for Patent Term Extension (the "Application") on September 30, 2009 relating to the above-captioned patent. Nissan respectfully requests that the Application be supplemented with the information described herein and attached hereto.

Section XVI of the Application includes an explanation that Nissan was not the marketing applicant before the Food and Drug Administration in IND 60,492 or NDA 022363. Sankyo Pharma Inc. (now Daiichi Sankyo, Inc.) ("Sankyo") was the marketing applicant in IND 60,492 from the time of filing until 2005. In 2005, Kowa Research Institute, Inc. ("KRI"), assumed ownership and became the marketing applicant in IND 60,492. In 2008, KRI filed NDA 022363 as the authorized agent of Kowa Company, Ltd. ("KCL"). KCL, through its

authorized agent KRI, was the marketing applicant in NDA 022363 through approval.

Exhibit E to the Application was a letter from KRI to the U.S. Patent and Trademark Office authorizing Nissan to rely on the activities of the marketing applicants before the Food and Drug Administration in IND 60,492 and NDA 022363.

Supplemental to the foregoing explanation, Nissan has attached hereto Exhibit F, which is a letter from Sankyo to the U.S. Patent and Trademark Office authorizing Nissan to rely on the activities of Sankyo before the Food and Drug Administration in connection with IND 60,492.

* * * *

Please direct any questions or comments regarding this submission to the undersigned.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Jacob A. Doughty
Registration No. 46,671

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)

Attachment:
Exhibit F

DAIICHI SANKYO, INC.
Two Hilton Court, Parsippany, NJ 07054
Tel 973 944 2600 Fax 973 944 2645

November 11, 2009

Ms. Mary Till
Office of Patent Legal Administration
U.S. Patent and Trademark Office
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Re: Application for Extension of Patent Term
For U.S. Patent No. 5,856,336

Dear Ms. Till:

Sankyo Pharma Inc., now Daiichi Sankyo, Inc., ("Daiichi Sankyo") was the applicant and IND holder before the Food and Drug Administration in regard to IND 60,492 (relating to Livalo® – film-coated tablets of pitavastatin calcium) from the time of filing until Kowa Research Institute, Inc., assumed ownership of IND 60,492 from Daiichi Sankyo in 2005. Daiichi Sankyo authorizes Nissan Chemical Industries, Ltd. ("Nissan"), to rely on the activities of Daiichi Sankyo as the applicant and IND holder in regard to IND 60,492 in connection with Nissan's application for extension of the term of U.S. Patent No. 5,856,336.

Very truly yours,

Craig B. Bleifer
Vice President, General Counsel & Secretary

Electronic Acknowledgement Receipt

EFS ID:	7307411
Application Number:	07883398
International Application Number:	
Confirmation Number:	3046
Title of Invention:	QUINOLINE TYPE MEVALONOLACTONES
First Named Inventor/Applicant Name:	YOSHIHIRO FUJIKAWA
Customer Number:	22850
Filer:	Marvin Jay Spivak/Michelle Munday
Filer Authorized By:	Marvin Jay Spivak
Attorney Docket Number:	49-168-0-DIV
Receipt Date:	29-MAR-2010
Filing Date:	15-MAY-1992
Time Stamp:	16:21:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		342163USPTE.PDF	137676 8d28faf4523e8260bbf80b5076f2a41506a8e07b	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Miscellaneous Incoming Letter	2	4
Warnings:			
Information:			
	Total Files Size (in bytes):	137676	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

MAY 20 2010

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

Dear Ms. Axelrad:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 5,856,336. The application was filed on September 30,2009, under 35 U.S.C. § 156.

The patent claims the human drug product LIVALO® and a method of using LIVALO®. LIVALO® was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Stephen G. Baxter
Jacob A. Doughty
Oblon Spivak McClelland Maier & Neustadt LLP
1940 Duke Street
Alexandria, VA 22314

RE: LIVALO® (pitavastatin calcium)
Docket No. FDA-2010-E-0042

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 28 2010

Re: LIVALO
Docket No.: FDA-2010-E-0042

The Honorable David J. Kappos
Undersecretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the application for patent term extension for U.S. Patent No. 5,856,336, filed by Nissan Chemical Industries, Ltd., under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the application and have determined the regulatory review period for LIVALO (pitavastatin calcium), the human drug product claimed by the patent.

The total length of the regulatory review period for LIVALO (pitavastatin calcium) is 3,341 days. Of this time, 3,036 days occurred during the testing phase and 305 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: June 12, 2000.

   The applicant claims June 9, 2000, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 12, 2000, which was 30 days after FDA receipt of the IND.

2. The date the application was initially submitted with respect to the human drug product under section 505 of the Federal Food, Drug, and Cosmetic Act: October 3, 2008.

   The applicant claims October 1, 2008, as the date the new drug application (NDA) for LIVALO (NDA 22-363) was initially submitted. However, FDA records indicate that NDA 22-363 was submitted on October 3, 2008.

3. The date the application was approved: August 3, 2009.

   FDA has verified the applicant's claim that NDA 22-363 was approved on August 3, 2009.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Stephen G. Baxter
Oblon, Spivak, McClelland, Maier & Neustadt, PC
Customer 22850
1940 Duke Street
Alexandria, VA 22314

Dated: October 22, 2010.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2010–31846 Filed 12–17–10; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–E–0042]

Determination of Regulatory Review Period for Purposes of Patent Extension; LIVALO

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for LIVALO and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit electronic comments to *http://www.regulations.gov*. Submit written petitions along with three copies and written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6222, Silver Spring, MD 20993–0002, 301–796–3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product LIVALO (pitavastatin calcium). LIVALO is indicated for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides, and to increase high-density lipoprotein cholesterol. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for LIVALO (U.S. Patent No. 5,856,336) from Nissan Chemical Industries, Ltd., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated March 3, 2010, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of LIVALO represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for LIVALO is 3,341 days. Of this time, 3,036 days occurred during the testing phase of the regulatory review period, while 305 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)) became effective:* June 12, 2000. The applicant claims June 9, 2000, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 12, 2000, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* October 3, 2008. The applicant claims October 1, 2008, as the date the new drug application (NDA) for LIVALO (NDA 22–363) was initially submitted. However, FDA records indicate that NDA 22–363 was submitted on October 3, 2008.

3. *The date the application was approved:* August 3, 2009. FDA has verified the applicant's claim that NDA 22–363 was approved on August 3, 2009.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,826 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (*see* **ADDRESSES**) either electronic or written comments and ask for a redetermination by February 18, 2011. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by June 20, 2011. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (*See* H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Interested persons may submit to the Division of Dockets Management (*see* **ADDRESSES**) electronic or written comments and written petitions. It is only necessary to send one set of comments. It is no longer necessary to send three copies of mailed comments. However, if you submit a written petition, you must submit three copies of the petition. Identify comments with the docket number found in brackets in the heading of this document. Comments and petitions that have not been made publicly available on regulations.gov may be viewed in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 22, 2010.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2010–31847 Filed 12–17–10; 8:45 am]

BILLING CODE 4160–01–P

Department of Health and Human Services | Public Health Service

Food and Drug Administration
Rockville, MD 20857

AUG 8 2011

Re: LIVALO
Docket No.: FDA-2010-E-0042

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the patent term extension application for U.S. Patent No. 5,856,336 filed by Nissan Chemical Industries, Ltd., under 35 U.S.C. § 156. The patent claims LIVALO (pitavastatin calcium), which was assigned new drug application (NDA) No. 22-363.

In the December 20, 2010, issue of the Federal Register (75 Fed. Reg. 79382), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before June 20, 2011, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Stephen G. Baxter
Oblon, Spivak, McClelland, Maier & Neustadt, PC
Customer 22850
1940 Duke Street
Alexandria, VA 22314