CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-363

SUMMARY REVIEW

8/3/09

Summary Basis for Regulatory Action

Date	August 3, 2009
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # **Supp #**	NDA 22-363
Applicant Name	Kowa Company Limited
Proprietary / Established (USAN) Names	Livalo pitavastatin
Dosage Forms / Strength	Tablets 1 mg, 2 mg, and 4 mg
Proposed Indication(s)	To reduce TC, LDL, Apo B, non-HDL, TG, TC/HDL ratio, Apo B/Apo AI ratio, and to increase HDL and Apo AI in subjects with primary hyperlipidemia or mixed dyslipidemia
Action:	*Approval*

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding pitavastatin and the reader should refer to the reviews in the action package for a more detailed discussion. Pitavastatin is an HMG-CoA reductase inhibitor (statin) that works the same as the six other statins already on the market.

Pitavastatin, as well as all the other statins, was evaluated for efficacy based on its effect on decreasing serum LDL. It should be noted that there is a wealth of cardiovascular outcome data from multiple trials regarding the use of statins for hyperlipidemia. Decreases in LDL has correlated, at least for the statin class, with positive cardiovascular results across the different drugs. For this application, pitavastatin was compared to other active statins in non-inferiority trials and found to be effective in lowering LDL.

As Dr. Colman notes, there are a couple of major safety concerns associated with statins use. The first is that it is well recognized that all statins can cause myopathy and even frank rhabdomyolysis. This finding has in some cases limited the upper dose or has led to marketing removal as exemplified by cerivastatin (Baycol). The second major safety concern is whether statins have a potential for liver toxicity because they all cause transaminitis. Early in statin development transaminitis was noted, but it was unclear if this would progress to actual liver dysfunction. Over the years, there has been little evidence that the use of statins and associated transaminitis actually lead to frank liver failure.

Pitavastatin was approved in Japan in 2003. As Dr. Colman notes, Japanese regulation require large, single-arm 2-year post-approval studies. In this case, approximately 20,000 Japanese subjects have been treated with 1 or 2 mg of pitavastatin without evidence of a significant

safety concern. Our own internal evaluation of the Japanese and clinical development data also did not find a significant signal of concern.

We now have several statin agents on the market, and there would be little tolerance for adding a new one if it had a significant safety signal not experienced by the other agents. That does not seem to be the case here and pitavastatin does enjoy a metabolism route avoiding CYP3A4 whereby it may have less drug-drug interactions than those agents that do utilize this route. In addition efficacy has been demonstrated. Therefore, I recommend approval of pitavastatin.

Efficacy

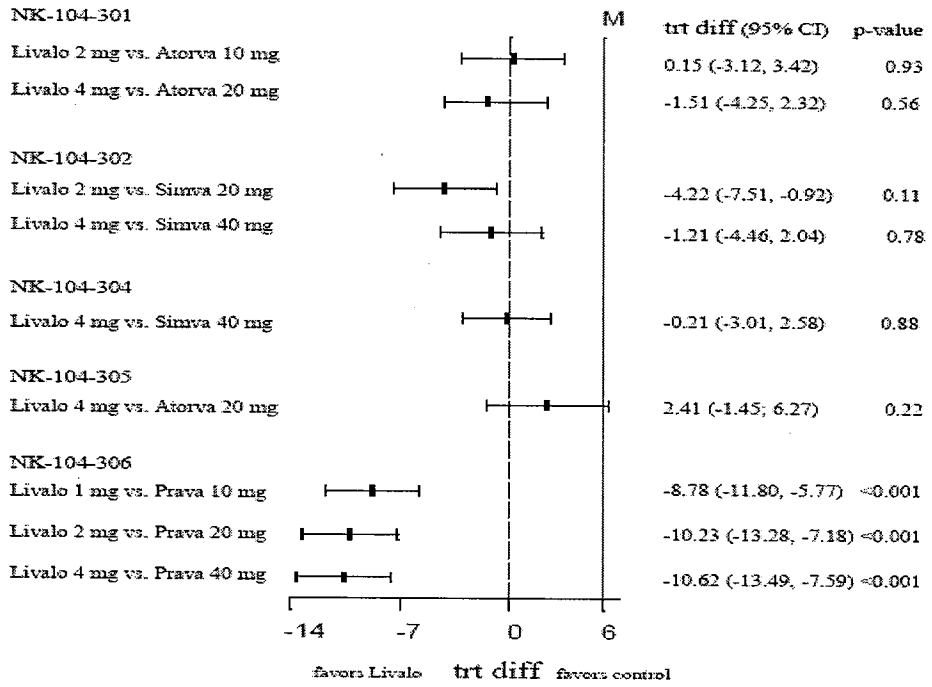
Efficacy has been thoroughly discussed in Drs. Gortler, Chowdhury and Colman's reviews. I agree with their conclusions and I will not repeat the specifics here. (b) (4) The efficacy of pitavastatin was compared to three marketed statins in exceeding a non-inferiority margin of 6% during the 12-week trials, although it should be noted that the maximal dose of the comparator was not used (atorvastatin 40mg and 80 mg, simvastatin and pravastatin 80mg were excluded). The following table and forest plot from Dr. Colman's review (Page 6), demonstrates the efficacy results for the randomized trials.

Mean Percent Change in LDL from Baseline to Endpoint – Phase 3 Trials						
	N	Baseline mg/dL	Week 12 mg/dL	% Change	Mean Diff vs. Comparator	p-value
Study 301						
Pita 2 mg	315	184	114	-38%	-0.15 (-3.4, 3.1)	0.9
Pita 4 mg	298	182	100	-45%	0.96 (-2.3, 4.2)	0.6
Atorva 10 mg	102	180	112	-38%	NA	
Atorva 20 mg	102	182	103	-44%	NA	
Study 302						
Pita 2 mg	307	184	112	-39%	4.1 (0.8, 7.3)	0.01
Pita 4 mg	319	184	103	-44%	1.1 (-2.1, 4.3)	0.5
Simva 20 mg	107	184	119	-35%	NA	
Simva 40 mg	110	184	105	-43%	NA	
Study 304						
Pita 4 mg	233	166	93	-44%	0.3 (-2.5, 3.1)	0.8
Simva 40 mg	118	167	93	-44%	NA	
Study 305						
Pita 4 mg	274	143	84	-41%	-2.3 (-6.2, 1.5)*	0.3
Atorva 20 mg	136	146	82	-43%		
Study 306						

Mean Percent Change in LDL from Baseline to Endpoint – Phase 3 Trials						
	N	Baseline mg/dL	Week 12 mg/dL	% Change	Mean Diff vs. Comparator	p-value
Pita 1 mg	207	164	112	-31	8.8 (5.8, 11.8)	<0.001
Pita 2 mg	224	163	99	-39	10.2 (7.2, 13.3)	<0.001
Pita 4 mg	210	164	91	-44	10.5 (7.4, 13.5)	<0.001
Prava 10 mg	103	164	127	-22	NA	
Prava 20 mg	96	164	116	-29	NA	
Prava 40 mg	102	167	110	-34	NA	

*Did not meet the -6% criterion for non-inferiority

The below figure taken from Dr. Lui's statistical review provides the LDL data in a forest plot. The solid vertical line denoted M indicates the 6% non-inferiority margin.



It appears that pitavastatin 1, 2 and 4 mg are effective in lowering LDL, and are non-inferior compared to low to medium-range doses of the comparator and even superior in the case of pravastatin (pravastatin 80 mg was not tested). One could speculate however that if the 4 mg dose of pitavastatin were to have been compared to the highest dose of atorvastatin or simvastatin, it may well have been inferior for LDL lowering. Changes in the secondary endpoints of total cholesterol, Apo B, TG, non-HDL, HDL and Apo A1 also reflected the findings above.

Safety

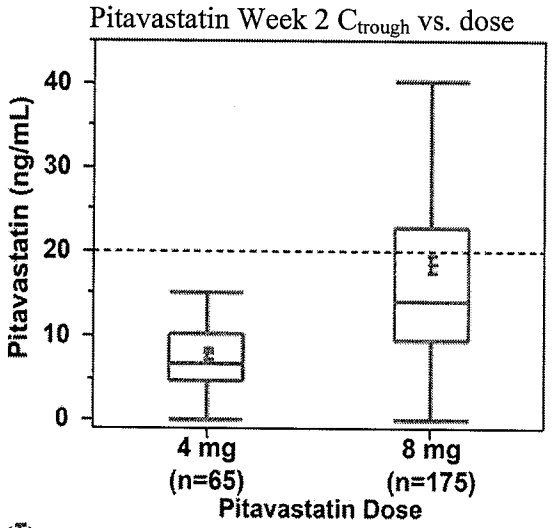
The available safety data and conclusions are outlined in Drs. Chowdhury and Colman's reviews and I agree with their conclusions. There is a considerable safety database for this

application, mainly because of the data from Japan, however there is not any placebo and little comparator controlled data beyond 12 or 16 weeks.

No cases of rhabdomyolysis (CPK >10x + muscle symptoms) were reported during the controlled phases of development with doses 4 mg or less. Dr. Colman's review has the table below (page 9) that compares CPK changes <10 x ULN of pitavastatin to placebo or comparator that had myopathy.

Percentage of Patients with CPK 1X to < 10XULN with Muscle Symptoms Core 12-Week Phase 2 and 3 Trials					
Treatment	**N**	**1 x to < 10 x ULN**	**Treatment**	**N**	**1 x to < 10 x ULN**
Placebo	208	5.3%	Atorva 10 mg	118	1.7%
Pita 1 mg	309	2.3%	Atorva 20 mg	240	2.1%
Pita 2 mg	951	1.5%	Atorva 40 mg	51	5.9%
Pita 4 mg	1540	1.8%	Atorva 80 mg	96	6.3%
Pita 8 mg	497	4.0%	Simva 20 mg	107	0.9%
Pita 16 mg	102	14.7%	Simva 40 mg	229	3.1%
Pita 32 mg	34	8.8%	Prava 10 mg	103	2.9%
Pita 64 mg	33	7.8%	Prava 20 mg	96	1.0%
			Prava 40 mg	102	1.0%

The incidence rates of asymptomatic CPK elevations were similar between pitavastatin and the comparators. Dr. Colman summarized Dr. Manoj Khurana's review on the degree of overlap one may expect between subjects taking pitavastatin 4 and 8 mg as the 75th percentile of the 4 mg group is below the 25th percentile for the 8 mg dose. This is represented graphically below (Dr. Colman's review, page 10).



(Ŧ) Mean (±SE), box represents the middle 50% of data with the solid line representing median

Note that the dotted horizontal line indicates the pitavastatin concentration above which two subjects taking pitavastatin 8 mg dose developed rhabdomyolysis.

Based on the totality of the clinical data, it would appear that the 1 mg to 4 mg doses of pitavastatin are not associated with increased risk for myopathy above those of low-to-moderate does of the comparators.

Dr. Colman has a thorough discussion of transaminitis associated with pitavastatin use, and has the following table (page 11) in which he notes the incidence rates of single ALT > 3 X ULN.

Incidence of ALT and Total Bilirubin Above Upper Limits of Normal – Placebo and Pitavastatin Core 12-Week Phase 2 and 3 Trials				
	Placebo	Pitavastatin		
	n=208	1mg n=309	2mg n=951	4mg n=1540
>3XULN	0	1 (0.3%)	5 (0.5%)	1 (0.1%)
>5XULN	0	0	2 (0.2%)	2 (0.1%)
>10XULN	0	1 (0.3%)	0	0
>20XULN	0	0	0	0
>3XULN with TB>2XULN	0	0	0	0

He notes in his summary that there is a greater incidence of transaminitis in subjects treated with 1 through 4 mg of pitavastatin compared with subjects treated with low-to-moderate doses of comparator statins and that this difference is unlikely to be of clinical significance. I agree that the transaminitis that is noted is unlikely to be of clinical significance, but would add to the consideration of whether the incidence is greater or not to comparators that transaminitis was a rare event and trying to evaluate if the incidence between pitavastatin and comparators is really different is difficult because the same numbers of subjects were not exposed between the group. Below is a table from Drs. Chowdhury and Gortler's review (page 97).

	Pitavastatin				**Atorvastatin**				**Simvastatin**		**Pravastatin**			
No.(%) Subjects Abnormal Results	**1mg N=309**	**2mg N=951**	**4mg N=1540**	**8mg N=479**	**10mg N=118**	**20mg N=240**	**40mg N=51**	**80mg N=96**	**20mg N=107**	**40mg N=229**	**10mg N=103**	**20mg N=96**	**40mg N=102**	**Placebo N=108**
>3XULN	1 (0.3)	5 (0.5)	1 (0.1)	4 (0.8)	0	0	0	0	0	1 (0.4)	0	0	0	0
>5XULN	0	2 (0.2)	2 (0.1)	1 (0.2)	0	0	0	0	0	0	0	0	0	0
>10XULN	1 (0.3)	0	0	0	0	0	0	1(1.0)	0	0	0	0	0	0
>20XULN	0	0	0	0	0	0	0	1(1.0)	0	0	0	0	0	0
ALT >3XULN with TB >1.5XULN	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ALT >3XULN with TB >2XULN	0	0	0	0	0	0	0	1(1.0)	0	0	0	0	0	0
Source: ISS, Table 1, page 16.														

From this table, one could contend that the number of subjects exposed to pitavastatin was many fold greater than those exposed to any of the comparators, affording pitavastatin greater 'opportunity' to find an individual that is genetically predisposed to express transaminitis

compared to the comparators. As an example, pitavastatin 4 mg was given to 1540 subjects, compared to 240 subjects taking atorvastatin 20 mg (an equivalent dose). While there were three events of ALT > 3 ULN in the pitavastatin 4 mg group, there was also a six-fold difference in the number of subjects exposed between equivalent doses with atorvastatin. As such, a small number of events may make the group with more exposures appear as if they have a higher rate when in fact if more subjects were exposed in the equivalent dose of atorvastatin, they could have easily have found 1 or 2 or 3 subjects that were genetically predisposed to have ALT elevations, making the incidence seem similar. Another way to look at it is that one could make the case that the 3 events in the pitavastatin 4 mg group should have been divided by 6 to see how that compares to the atorvastatin 20 mg group, which would give less than one event. Such is the dilemma whenever we deal with a small number of events, and differential numbers of subjects exposed between active agent and comparator. I believe that when dealing with a small number of events, as above, it is difficult to draw any conclusions regarding whether one drug has a higher incidence rate than another when there is not an equivalent number of subjects exposed. In cases like this, we usually err on the side of caution, and clearly if there had been a Hy's law case in the pitavastatin group, we would be reluctant to approve. However, transaminitis is a known manifestation of statin use and does not seem to lead to clinical consequence. Bearing this in mind, I agree that it does not appear that pitavastatin use is associated with hepatotoxicity beyond the transaminitis that all statins exhibit and the discussion of whether transaminitis is greater with pitavastatin is really an academic exercise. Noted in all the reviews is that the one subject in the pitavastatin 1 mg dosage arm with ALT > 10 ULN had acute cholecystitis and the subject taking atorvastatin 80 mg that had ALT > 3 ULN and T Bili > 2 ULN had hepatitis C.

Advisory Committee Meeting

An advisory committee meeting was not held as we have a great deal of experience with statin agents and pitavastatin does not appear to have any significant safety or efficacy issues that are different from our prior experience.

Conclusions and Recommendations

Pitavastatin demonstrated efficacy in decreasing LDL as expected with a statin agent. The safety profile appears similar to all the other marketed agents. I recommend approval for the treatment of primary hyperlipidemia and mixed dyslipidemia.

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

3/3/09

Summary Review for Regulatory Action

Date	July 12, 2009
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	22-363
Applicant Name	Kowa Company Limited
Date of Submission	October 4, 2008
PDUFA Goal Date	August 4, 2009
Proprietary Name / Established (USAN) Name	Livalo/pitavastatin
Dosage Forms / Strength	1 mg, 2 mg, and 4 mg tablets
Proposed Indication(s)	To reduce TC, LDL, Apo B, non-HDL, TG, TC/HDL ratio, Apo B/Apo AI ratio, and to increase HDL and Apo AI in subjects with primary hyperlipidemia or mixed dyslipidemia
Recommended Action for NME:	Approve

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Iffat Chowdhury, MD, and David Gortler, PharmD
Statistical Review	Wei Liu, PhD
Pharmacology Toxicology Review	Lee Elmore, PhD
CMC Review/OBP Review	Olen Stephens, PhD, and Houda Mahayni, PhD
Microbiology Review	Not Applicable
Clinical Pharmacology Review	Johnny Lau, PhD
DDMAC	Not Applicable
DSI	Michael Rashti
CDTL Review	See Deputy Division Director Memo
OSE/DMEPA	Denise Baugh, PharmD
OSE/DDRE	Not Applicable
OSE/DSRCS	Not Applicable
Thorough QT Consult	Joanne Zhang, PhD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This submission provides efficacy and safety data in support of approval of pitavastatin 1 mg, 2 mg, and 4 mg once-daily for the treatment of primary hyperlipidemia and mixed dyslipidemia in adults. (b) (4) There have been no significant disagreements between reviewers or review disciplines with respect to data interpretation or regulatory recommendations.

2. Background

Six statins are marketed in the U.S.: lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), atorvastatin (Lipitor), and rosuvastatin (Crestor). Cerivastatin (Baycol) was removed from the market in 2001 due to an inordinately high incidence of myopathy relative to other statins.

Given the irrefutable evidence that statins reduce the risk for cardiovascular disease events in a wide range of patient populations, it was considered more appropriate to use active comparators rather than placebo groups in the pitavastatin phase 3 trials. The active comparators used were atorvastatin (Lipitor), simvastatin (Zocor), and pravastatin (Pravachol). Rosuvastatin (Crestor) was not included in the phase 3 trials. Atorvastatin and simvastatin are the most commonly prescribed statins in the U.S.

At a September 20, 2005 End-of-Phase 2 meeting, the Division recommended that the highest approved doses of the comparator statins be included in the phase 3 pitavastatin studies. However, Kowa opted not to follow this recommendation and did not include the 40 mg or 80 mg doses of atorvastatin or the 80 mg dose of simvastatin or pravastatin in their phase 3 trials. I believe this shortcoming should be noted in the pitavastatin labeling and perhaps all advertisement. The average LDL lowering associated with atorvastatin 40 mg or 80 mg, simvastatin 80 mg, and rosuvastatin 20 mg or 40 mg exceeds that observed with pitavastatin 4 mg.

All marketed statins were approved based on changes in serum LDL. The Division considers LDL a validated surrogate for cardiovascular disease. In the absence of evidence that a drug adversely affects one or more lipid parameters or is associated with serious off-target toxicity, approval of a LDL-lowering compound may be based on favorable changes in LDL rather than cardiovascular outcomes data. Given the wealth of positive cardiovascular outcomes data with statins, I believe that it is appropriate to base approval of pitavastatin on changes in LDL. The labeling will include a disclaimer that the effects of pitavastatin on cardiovascular morbidity and mortality have not been studied.

Upon agreement between Kowa and the Division, a LDL non-inferiority margin of 6% was used in the pitavastatin phase 3 studies. When the dose of a statin is doubled, LDL often

decreases by approximately 6%. This is the reason that a non-inferiority margin of 6% has been used in previous statin trials and was used in the pitavastatin trials. A LDL non-inferiority margin calculated in the typical manner (e.g., preserving 50% of the treatment effect based on historical statin and placebo data) would be much larger than 6%. Since the relationship between LDL level and risk for cardiovascular disease is linear over a wide range of LDL values, it is difficult to define a minimally important effect, as is the goal when defining a non-inferiority margin. Even a 1% decrease in LDL could be considered clinically important. Nonetheless, from a practical standpoint I agree with the use of a LDL non-inferiority margin of 6%.

The major safety issues with statins are myopathy and transaminitis with concern for possible hepatotoxicity. Proteinuria was raised as a potential safety issue during the review of the rosuvastatin New Drug Application. All statin labels discuss the risk of myopathy and recommend periodic monitoring of serum transaminase levels. (b) (4)

During the conduct of two phase 2 pitavastatin studies nine (1.4%) subjects developed "rhabdomyolysis" or CPK levels $\geq$ 10 x the upper limit of normal (ULN). Because all nine cases occurred in subjects treated with pitavastatin doses of 8 mg or higher, (b) (4)

Pitavastatin 1 mg, 2 mg, and 4 mg doses were approved in Japan for the treatment of dyslipidemia in 2003. Per routine Japanese regulations, Kowa was required to conduct an open-label, single-arm 2-year post-approval study of pitavastatin in approximately 20,000 patients. Nearly all subjects were treated with 1 mg or 2 mg of pitavastatin. The most commonly reported reactions were increased CPK (2.7%), increased ALT (1.8%), and increased AST (1.5%). Rhabdomyolysis was reported in 2 subjects (0.01%), although the diagnosis in one case is questionable as the subject's CPK value was below 10 x ULN. Proteinuria was reported for 5 subjects (0.03%) and renal failure in 1 subject (0.01%). Hepatic function abnormal was recorded for 6 subjects (0.03%), liver disorder for 4 subjects (0.02%), and jaundice in 1 subject (0.01%). There were no cases of liver failure or transplant reported. Although uncontrolled, these data do not raise concern about the safety of the 1 mg and 2 mg doses of pitavastatin.

In response to a June 24, 2009, inquiry from the Division, the Japanese drug regulatory authorities remarked that they do not have any specific concerns regarding pitavastatin's safety profile relative to other marketed statins in that country. Statins approved in Japan include fluvastatin, simvastatin, pravastatin, atorvastatin, pitavastatin, and rosuvastatin.

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. On July 15, 2009, the Office of

Compliance concluded that the manufacturing site inspections were acceptable. A biowaiver for the 1 mg pitavastatin dose was granted

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

In his review of the toxicology data, Dr. Elmore notes that renal toxicity was observed in rats that received 8-hydroxypitavastatin 200 mg/kg/day BID orally for two weeks or 400 mg/kg/day BID orally for one week. Eight-hydroxypitavastatin is a minor metabolite of pitavastatin that is not formed in-vivo in rats. In a 7-day clinical study in which subjects received 4 mg daily of pitavastatin, the levels of 8-hydroxypitavastatin were below the limit of detection (0.5 ng/mL) in five of seven subjects. In two subjects, 8-hydroxypitavastatin was measured at a concentration of 0.6 ng/mL. Given the very high doses of 8-hydroxypitavastatin used in the rat studies and the very low plasma levels of 8-hydroxypitavastatin observed in humans administered 4 mg daily of pitavastatin, I do not believe that the renal toxicity noted in the rats administered 8-hyroxypitavastatin is of clinical significance.

5. Clinical Pharmacology

Pitavastatin is metabolized into two principal metabolites, pitavastatin lactone (major) and 8-hydroxypitavastatin (minor). Parent pitavastatin is not significantly metabolized by CYP3A4. Pitavastatin lactone metabolism involves glucuronidation and 8-hydronxypitavastatin metabolism involves the activity of CYP2C9. The half-life of pitavastatin is approximately 8 – 12 hours.

Through inhibition of hepatic uptake of pitavastatin, cyclosporine and erythromycin increase the extent of exposure to concomitantly administered pitavastatin by ~ 5-fold and 3-fold, respectively. Gemfibrozil, fenofibrate, atazanavir, and grapefruit juice do not appreciably increase the rate or extent of exposure to pitavastatin. Compared with lovastatin, simvastatin, and atorvastatin – statins metabolized by CYP3A4 – pitavastatin has a low potential for clinically significant drug-drug interactions.

The clinical pharmacology review team recommends that Kowa conduct an interaction study with pitavastatin and the protease inhibitors, lopinavir and ritonavir. These two compounds have been shown to increase the AUC and C_{max} of rosuvastatin by 2- and 5-fold, respectively. Pitavastatin's PK profile is very similar to rosuvastatin's. I agree with this recommendation and believe the study should be a post-marketing requirement.

In patients with moderate renal impairment and end stage renal disease receiving dialysis, the pitavastatin AUC was 79% and 86% higher, respectively, compared with healthy volunteers. (b) (4) patients with severe renal impairment *not receiving dialysis* had a 3-fold increase in the AUC for rosuvastatin, I believe Kowa should examine the PK profile of pitavastatin in patients with severe renal impairment (b) (4) The study should be a post-marketing requirement.

No clinically meaningful increases in QTc were observed in subjects treated with pitavastatin 4 mg or 16 mg in a thorough QT study. The results of this study have been reviewed by FDA's Interdisciplinary Review Team for QT Studies. This group noted that exposure to pitavastatin might exceed that observed with the 16 mg dose when a patient takes 4 mg concomitantly with cyclosporine, which may increase pitavastatin exposure by up to 5-fold. However, the weight of evidence does not suggest that pitavastatin or statins as a class are associated with prolongation of the QTc interval. I do not believe that the use of the 16 mg dose of pitavastatin rather than a higher dose in the thorough QT study is a significant shortcoming.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The efficacy and safety data from 12 to 16-week, placebo- and active-controlled phase 2 and phase 3 clinical studies (Group 1 in the primary review) were the focus of Drs. Chowdhury's and Gortler's reviews. The sponsor did conduct four extention studies, but most of the data from these studies involve uncontrolled, open-label exposure to pitavastatin. This summary review likewise focuses on the 12 to 16-week placebo- and active-controlled phase 2 and 3 data, as these provide the most valid assessments of pitavastatin's absolute and relative efficacy and safety.

Kowa conducted five phase 2 studies of pitavastatin. Three of the studies were terminated early due to an increased incidence of myopathy with doses of 8 mg or more. Dr. Gortler's review of phase 2 efficacy data is primarily based on the placebo-controlled, dose-ranging 12-week studies 202 and 203.

The primary efficacy endpoint in these studies was change in LDL. As shown in the table below, pitavastatin reduced levels of LDL in a dose-related manner in subjects with primary hyperlipidemia. All active doses significantly reduced LDL compared with placebo.

Mean Percent Change in LDL from Baseline to Week 12 – Study 2.02				
	Placebo N=53	Pit 1 mg N=52	Pit 2 mg N=49	Pit 4 mg N=51
Baseline LDL	5.1 mmol/L	5.1 mmol/L	5.2 mmol/L	5.1 mmol/L
Mean % Change	-3%	-32%	-36%	-43%

Values obtained from Dr. Lui's statistical review; $p<0.001$ for all comparison of pitavastatin vs. placebo

The changes in total cholesterol (TC), Apo B, and triglycerides (TG) were also dose-related and favorable relative to the changes observed with placebo. Although the increases in high density lipoprotein (HDL) levels were statistically significantly greater in all of the pitavastatin groups vs. the placebo group, there was not a dose-related increase among the pitavastatin groups. This finding is consistent with data for other statins.

Results were similar in a second phase 2 study (203) which evaluated pitavastatin's effects in subjects with mixed dyslipidemia.

The efficacy of pitavastatin vs. three marketed statins was evaluated in five 12-week phase 3 trials, designated: 301, 302, 304, 305, and 306. The primary intent of these trials was to assess, in subjects with primary hyperlipidemia or mixed dyslipidemia, pitavastatin's LDL-lowering efficacy following 12 weeks of treatment relative to atorvastatin, simvastatin, and pravastatin using a non-inferiority margin of 6%. The 1 mg dose of pitavastatin was compared with pravastatin 10 mg; the 2 mg dose of pitavastatin was compared with pravastatin 20 mg, atorvastatin 10 mg, and simvastatin 20 mg; and the 4 mg dose of pitavastatin was compared with pravastatin 40 mg, atorvastatin 20 mg, and simvastatin 40 mg.

The baseline demographic characteristics were similar among treatment groups within each trial. Aside from study 306, the mean age was approximately 60 years. The percentage of males and females was similar overall and most of the participants were Caucasian. The majority of subjects had primary hyperlipidemia. Trial 305 only enrolled subjects with type 2 diabetes and trial 306 enrolled elderly subjects. Roughly 90 to 95% of the subjects in the five trials completed the 12 weeks of treatment.

The mean percent changes in LDL in the five phase 3 trials are provided in the following table.

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Pita 2 mg	315	184	114	-38%	-0.15 (-3.4, 3.1)	0.9
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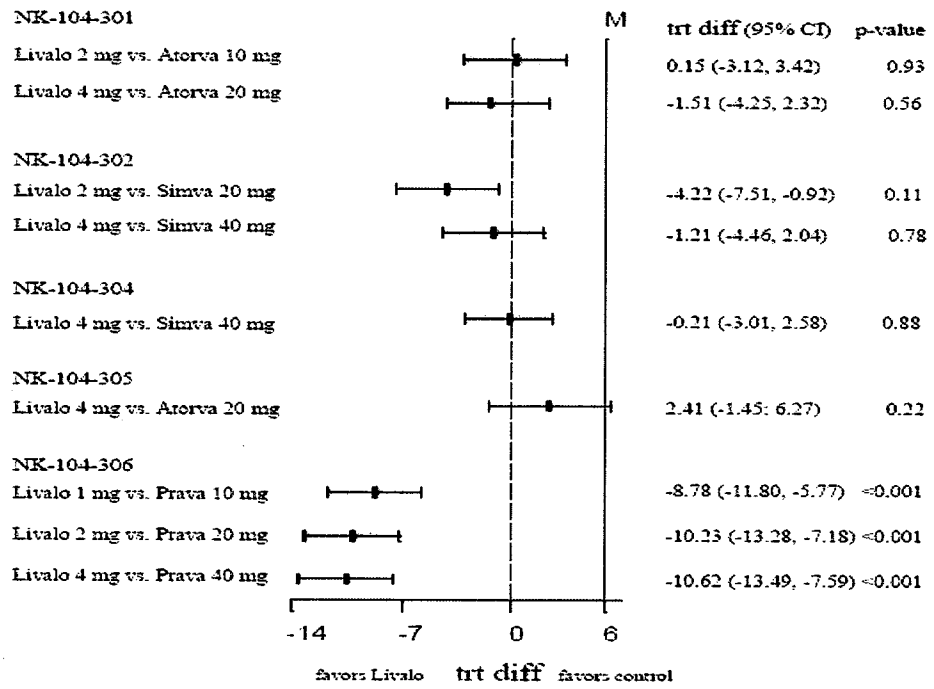
Prava 20 mg	96	164	116	-29	NA	
Prava 40 mg	102	167	110	-34	NA	

*Did not meet the -6% criterion for non-inferiority

The below figure taken from Dr. Lui's statistical review provides the LDL data in a forest plot. The solid vertical line denoted M indicates the 6% non-inferiority margin.



The LDL data from the five phase 3 active-controlled trials can be summarized as follows:

- Pitavastatin 1 mg, 2 mg, and 4 mg lower LDL by approximately 28%, 31%, and 41%, respectively. This degree of LDL lowering would be expected to reduce the risk for major cardiovascular events by approximately 25% to 40%.
- Pitavastatin 1 mg is superior to pravastatin 10 mg in elderly subjects.
- Pitavastatin 2 mg is non-inferior to atorvastatin 10 mg and superior to simvastatin 20 mg and pravastatin 20 mg in non-diabetic patients with primary hyperlipidemia or mixed dyslipidemia.

- Pitavastatin 4 mg is non-inferior to atorvastatin 20 mg and simvastatin 40 mg and is superior to pravastatin 40 mg in non-diabetic subjects with primary hyperlipidemia or mixed dyslipidemia.
- Pitavastatin 4 mg is not non-inferior to atorvastatin 20 mg in patients with type 2 diabetes.

The principal secondary efficacy endpoints included TC, Apo B, TG, non-HDL, HDL, and Apo A1. Non-inferiority margins were not defined for secondary efficacy endpoints. In general, the changes in the secondary efficacy endpoints were favorable with pitavastatin treatment and similar in magnitude to the changes observed with the comparator statins. As noted in the phase 2 studies, levels of HDL did not increase in a dose-related manner with pitavastatin (or the comparator statins).

The long-term efficacy of pitavastatin was evaluated in several studies, including study 307. Study 307 was a 52-week, open-label investigation that enrolled subjects who completed studies 301 and 302. All subjects were treated with 4 mg of pitavastatin regardless of their treatment in studies 301 and 302. Results of this study indicate that the lipid-altering effects of pitavastatin are maintained long-term, as expected.

Dr. Liu confirmed the validity of the sponsor's efficacy analyses.

8. Safety

Dr. Chowdhury's safety assessment of pitavastatin is based on data from five phase 2 clinical trials, five phase 3 clinical trials, and four open-label extension studies. Data from a 20,000 patient observational study from Japan were also taken into consideration when assessing pitavastatin safety.

As shown below, patient exposure was greatest for the 4 mg dose of pitavastatin during the phase 2, phase 3, and open-label extension studies.

Patient Exposure During Phase 2, Phase 3 and Extension Studies			
Treatment Group	**N**	**Mean Exposure (weeks)**	**Patient-Years**
Pitavastatin			
1 mg	309	12	69
2 mg	2562	17	824
4 mg	2406	37	1729
Atorvastatin			
10 mg	394	7	50
20 mg	264	12	59
40 mg	54	7	8
Simvastatin			
20 mg	336	7	42
40 mg	219	18	75
80 mg	5	36	4
Pravastatin			
10 mg	103	11	22

Patient Exposure During Phase 2, Phase 3 and Extension Studies			
Treatment Group	**N**	**Mean Exposure (weeks)**	**Patient-Years**
20 mg	198	8	29
40 mg	96	8	15

There are no placebo and little active-comparator data beyond 12 weeks of pitavastatin treatment. Hence, the most rigorous assessment of pitavastatin's safety comes from the 12-week phase 2 and 3 studies. The data from the extension studies are of minimal value.

The principal safety concern with statins is myopathy. The most serious form of myopathy is rhabdomyolysis, which is defined in multiple ways. Some define rhabdomyolysis as CPK > 10XULN even in the absence of muscle symptoms, whereas other define rhabdomyolysis as CPK > 10XULN with muscle symptoms and an increase in serum creatinine (usually with brown urine and urinary myoglobin). Additional definitions of rhabdomyolysis can be found in the medical literature.

During conduct of two phase 2 pitavastatin studies (209 and 2204), a total of 9 out of 648 (1.4%) subjects exposed to 8 mg to 64 mg of pitavastatin were coded as having developed rhabdomyolysis using MedDRA terminology: 2 subjects in the 8 mg group, 1 subject in the 16 mg group, 3 subjects in the 32 mg group, and 3 subjects in the 64 mg group. Seven of the nine cases met the study definitions of rhabdomyolysis and two of the nine cases (one on 32 mg and one on 64 mg) met a more stringent definition of rhabdomyolysis: muscle symptoms with CPK > 10XULN and serum creatinine elevation. All nine cases came to clinical attention within approximately three weeks of drug initiation. Based on these data, continued development of pitavastatin was limited to doses of up to 4 mg. Dr. Chowdhury's review provides a detailed account of these nine cases of myopathy/rhabdomyolysis.

No cases of rhabdomyolysis or CPK >10XULN with muscle symptoms were reported in any subject treated with placebo, pitavastatin 1 mg, 2 mg, or 4 mg or active comparator during the controlled phase 2 or phase 3 studies. The incidence rates of CPK >10XULN with muscle symptoms in subjects treated with pitavastatin 8 mg, 16 mg, 32 mg, and 64 mg were 0.4%, 1.0%, 6.0%, and 6.1%, respectively.

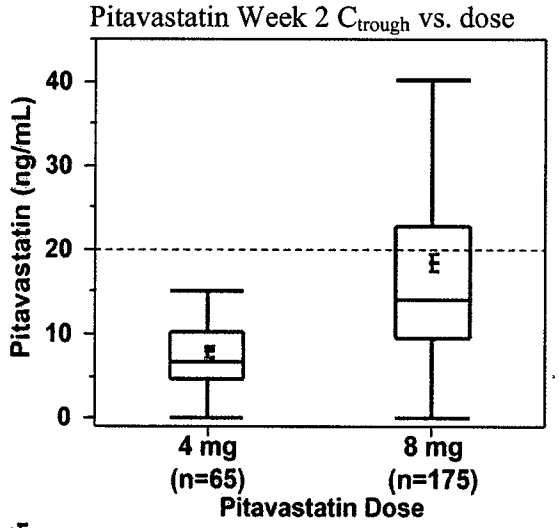
The following two tables provide the percentage of patients with CPK values 1X to < 10X ULN accompanied by muscle symptoms in the 12-week phase 2 and phases 3 trials.

Percentage of Patients with CPK 1X to < 10XULN with Muscle Symptoms Core 12-Week Phase 2 and 3 Trials					
Treatment	**N**	**1 x to < 10 x ULN**	**Treatment**	**N**	**1 x to < 10 x ULN**
Placebo	208	5.3%	Atorva 10 mg	118	1.7%
Pita 1 mg	309	2.3%	Atorva 20 mg	240	2.1%
Pita 2 mg	951	1.5%	Atorva 40 mg	51	5.9%
Pita 4 mg	1540	1.8%	Atorva 80 mg	96	6.3%
Pita 8 mg	497	4.0%	Simva 20 mg	107	0.9%
Pita 16 mg	102	14.7%	Simva 40 mg	229	3.1%
Pita 32 mg	34	8.8%	Prava 10 mg	103	2.9%
Pita 64 mg	33	7.8%	Prava 20 mg	96	1.0%
			Prava 40 mg	102	1.0%

Although the incidence rates of asymptomatic CPK values 1X to < 10XULN were much higher in the placebo, pitavastatin, and comparator groups than the rates for symptomatic CPK elevations, there were no differences of concern between the placebo and pitavastatin groups or between the pitavastatin and active comparator groups.

The incidence of patient-reported myalgia was 1.4% with placebo, 1.9% with pitavastatin 1 mg, 2.8% with pitavastatin 2 mg, and 3.1% with pitavastatin 4 mg. The numbers in the mid-to-high dose comparators were as follows: 2.0% with atorvastatin 40 mg, 8.3% with atorvastatin 80 mg, 3.9% with simvastatin 40 mg, and 2.9% with pravastatin 40 mg.

Because all cases of rhabdomyolysis in the phase 2 studies occurred in subjects treated with 8 mg or more of pitavastatin, Dr. Manoj Khurana, clinical pharmacology reviewer, examined the degree of overlap in serum pitavastatin levels between subjects treated with 8 mg and 4 mg of pitavastatin. As shown in the figure below, the 75th percentile for parent pitavastatin concentration in the 4 mg group is below the 25th percentile for pitavastatin concentration in the 8 mg group. The dotted horizontal line indicates the serum pitavastatin concentration (20 ng/mL) in two subjects who developed rhabdomyolysis on pitavastatin 8 mg. None of the subjects dosed with 4 mg pitavastatin had serum drug concentrations near 20 ng/mL. Results are similar for pitavastatin lactone, the major metabolite.



(Ŧ) Mean (±SE), box represents the middle 50% of data with the solid line representing median

Based on the clinical data provided in this NDA, the 1 to 4 mg doses of pitavastatin do not appear to be associated with an increased risk for myopathy relative to placebo or to low-to-moderate doses of atorvastatin, simvastatin, or pravastatin.

Statins are generally associated with a dose-related increase in the incidence of transaminitis (ALT and AST), presumably of hepatic origin. Most authorities, however, do not believe that the transaminitis signals risk for severe liver injury. According to some analyses, the incidence of severe hepatotoxicity associated with statins does not differ from the rate of idiopathic liver failure in the general population (~ 1 per 1,000,000 per-years). The Division and the Office of

Surveillance and Epidemiology are currently reviewing available data on statins and severe liver injury. Class labeling changes for hepatic transaminase monitoring for the statins may be in order following review of the available data.

The incidence rates of a single ALT > 3XULN during conduct of the phase 2 and 3 controlled pitavastatin studies were 0.3%, 0.5%, 0.1% in the 1 mg, 2 mg, and 4 mg pitavastatin groups, respectively (Table below).

Incidence of ALT and Total Bilirubin Above Upper Limits of Normal – Placebo and Pitavastatin Core 12-Week Phase 2 and 3 Trials				
	Placebo	Pitavastatin		
	n=208	1mg n=309	2mg n=951	4mg n=1540
>3XULN	0	1 (0.3%)	5 (0.5%)	1 (0.1%)
>5XULN	0	0	2 (0.2%)	2 (0.1%)
>10XULN	0	1 (0.3%)	0	0
>20XULN	0	0	0	0
>3XULN with TB>2XULN	0	0	0	0

The subject in the pitavastatin 1 mg group who developed an ALT >10XULN was diagnosed with acute cholecystitis due to gallstones.

With respective to the comparator statin groups, one subject treated with simvastatin 40 mg (0.4%) developed a single ALT > 3XULN. One subject in the 80 mg atorvastatin group (1.0%) developed an ALT value > 10XULN. In addition, a single subject in the 80 mg atorvastatin group developed an ALT > 20XULN with a total bilirubin >2XULN.

One subject (#5108-047) on pitavastatin 4 mg developed an ALT>10XULN with a total bilirubin >1.5XULN (and a slightly elevated alkaline phosphatase) during one of the extension studies. This was a 67-year-old woman with type II diabetes who received pitavastatin 4 mg from October 2006 to January 2007 during Study 305. She entered an extension study immediately following participation in Study 305 and remained on pitavastatin 4 mg. Concomitant medications included metformin, metoprolol, molsidomine, cilazapril, and amlodipine. One April 25, 2007, 113 days after starting in the extension study, the subject had an ALT=363 U/L (>10XULN), an AST 455 U/L (>20XULN), a bilirubin=2.07 mg/dL (>1.5XULN), and an Alk Phos=96 (slightly elevated). At this time, the patient reported a single episode of diarrhea. Pitavastatin was discontinued on April 26, 2007. On the following day, the subject's ALT was 253 U/L, her AST was 131 U/L, and bilirubin was 0.6 mg/dL. CPK was reported to be 516 U/L (normal <145 U/L). An abdominal ultrasound was unremarkable. HBs antigen was negative, as were antibodies to MCV. Over the next week, the subject's laboratory values declined and were reported as normal on May 8, 2007. The investigator considered a viral infection of the gastrointestinal tract as the cause of the transaminitis and elevated bilirubin. Pitavastatin was re-introduced on May 11, 2007, and the subject's ALT, AST, and bilirubin levels remained normal for approximately 20 additional weeks of treatment. It is unlikely that pitavastatin caused this patient's transaminitis and elevated bilirubin level.

There were no cases of liver failure or Hy's Law in any of the subjects treated with pitavastatin or active comparator. Although the incidence of transaminitis was higher in the pitavastatin groups vs. the comparator statin groups, there was no dose-response in the pitavastatin groups and the overall rate was very low.

The Office of Surveillance and Epidemiology reviewed 50 cases of Japanese post-marketing reports of possible liver injury associated with pitavastatin. They determined that there was insufficient evidence to conclude that pitavastatin is hepatotoxic. It was recommended that the sponsor submit all possible liver injury reports in an expedited manner for three years post-approval.

Proteinuria was identified as a potential safety concern during the review of the rosuvastatin New Drug Application. Kowa was therefore asked to measure the urinary protein/urinary creatinine ratio at baseline and endpoint in a subset of subjects participating in the phase 3 pitavastatin trials.

The mean change from baseline to endpoint in urine protein/creatinine ratio was greater in the two pitavastatin groups compared with the comparator statin groups (table below). It is noteworthy that the baseline values were higher in the two pitavastatin groups relative to the comparator groups.

Mean Change in Urine Protein/Urine Creatinine Ratio
Core 12-Week Phase 2 and 3 Trials

	Pita 2 mg	Pita 4 mg	Simva 20 mg	Simva 40 mg	Atorva 10 mg	Atorva 20 mg
	N=55	N=175	N=7	N=30	N=13	N=54
Baseline	0.14	0.10	0.08	0.07	0.07	0.09
Mean Change	0.17	0.18	0.12	0.001	0.11	0.05

In an analysis of outliers, the percentage of subjects who went from a normal urine protein/creatinine ratio (< 0.26) to an abnormal value (≥ 0.5) was 5.5% and 1.1% in the pitavastatin 2 mg and 4 mg groups, respectively, and 14.3%, 0%, 7.7%, and 3.7% in the simvastatin 20 mg, simvastatin 40 mg, atorvastatin 10 mg, and atorvastatin 20 mg groups, respectively.

Keeping in mind the extent of patient exposure to placebo, pitavastatin, and comparator statins in this NDA, the safety profile of pitavastatin can be summarized as follows:

- The 8 through 64 mg doses of pitavastatin are associated with an unacceptable risk for myopathy/rhabdomyopathy.
- There is little overlap in serum pitavastatin levels between subjects exposed to 4 mg vs. 8 mg pitavastatin.
- The 1 through 4 mg doses of pitavastatin do not appear to be associated with an excess risk for myopathy relative to low-to-moderate doses of atorvastatin, simvastatin, and pravastatin.
- There is a greater incidence of transaminitis in subjects treated with 1 through 4 mg of pitavastatin compared with subjects treated with low-to-moderate doses of comparator statins. This difference is unlikely to be of clinical significance.

- There were no cases of severe liver injury of Hy's Law in subjects treated with pitavastatin.
- There is no evidence that pitavastatin 1 through 4 mg is associated with clinically significant proteinuria compared with low-to-moderate doses of comparator statins.

9. Advisory Committee Meeting

Because pitavastatin is the 8th statin submitted for approval to the FDA and there were no significant efficacy or safety issues identified during review of the NDA, an advisory committee meeting was not considered necessary.

10. Pediatrics

Pediatric studies have been conducted for all six marketed statins. Because pitavastatin does not provide any advantages over available statins, the Division granted Kowa a full waiver for pediatric studies. Perc agreed with this decision.

11. Other Relevant Regulatory Issues

Dr. Chowdhury reviewed the financial disclosure information provided by the sponsor and concluded that there were no financial interests or arrangements between the applicant and the clinical investigators. The Division of Scientific Investigations concluded that the audited clinical sites and the clinical pharmacology site adequately adhered to the study protocols. The Division of Drug Marketing and Communication stated that they do not have any concerns regarding the promotional aspects of the proposed tradename, Livalo. The Division of Medication Error Prevention and Analysis found the proposed tradename acceptable with respect to the potential for medication errors.

12. Labeling

I agree with my colleagues in the Office of Surveillance and Epidemiology that the proposed tradename, Livalo, is not inappropriately promotional. I also agree that the tradename does not appear to pose a significant risk for medication errors due to look-alike or sound-alike drugs currently on the market. As of this writing, labeling negotiations with the sponsor are ongoing.

13. Decision/Action/Risk Benefit Assessment

Based on data submitted in this NDA and on correspondences the Divisions has had with the Japanese regulatory authorities, I believe the benefits of treatment with 1 mg, 2 mg, or 4 mg pitavastatin will outweigh any risks associated with this statin. I agree with the individual discipline reviewers that pitavastatin should be approved for the treatment of primary hyperlipidemia and mixed dyslipidemia.

The Division is mandating, through post-marketing requirements, that Kowa conduct 1) a PK interaction study with pitavastatin and the protease inhibitors, lopinavir and ritonavir, and 2) a PK study of pitavastatin in patients with severe renal impairment [(b) (4)] Data from these studies will provide important safety information for healthcare providers.

The Office of Surveillance and Epidemiology recommends that Kowa submit, in an expedited manner, all possible liver injury reports during the first three years post-approval. I agree with this recommendation and believe the sponsor should do the same for possible cases of rhabdomyolysis.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22363	ORIG 1		LIVALO TABLETS

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/s/

ERIC C COLMAN
08/03/2009