

Toxicity summary:**Lens toxicities**

Cataracts were seen in dogs in repeat dose studies at ≥ 3 mg/kg/day in a 13 week study and at ≥ 1 mg/kg/day in the 12 month study (2-fold human exposure based on AUC at 4 mg/day). This finding has been associated with statin treated dogs. Distribution studies indicate that the dog lens has a higher level of pitavastatin than other species with a rank order of distribution in the lens-to-plasma ratio of: dog (0.6) > mouse (0.54) > monkey (0.18) \approx rat (0.17) > rabbit (0.06). The lens-to-plasma ratio in humans is 0.05-0.17. Although ocular opacities were observed in a mouse study at 13-weeks at ≥ 75 mg/kg/day, it was not seen at the same dose following lifetime exposure in a 92 week carcinogenicity study. Lens concentrations of pitavastatin at 4 mg/day were 7 ng/g, which is below the concentration range in dogs of 123-616 ng/g that led to the formation of cataracts after daily oral dosing at 3 or 12-months. These data, in addition to the known association of statin exposure and cataracts in dogs, suggest that the dog lens is particularly hypersensitive to the distribution of HMG-CoA reductase inhibitors.

Renal toxicities

Renal toxicities were seen in male and female monkeys in 1 month and 6 month toxicology studies. Findings consisted of mild swelling of the proximal tubule epithelium with slight desquamation of tubular epithelium at ≥ 6 mg/kg/day (≥ 8.7 -fold MRHD at a 4 mg/day dose) in conjunction with increased kidney weight. Lower doses showed this finding, but toxicities were recoverable by 2 months post-withdrawal. Creatinine and blood urea nitrogen or phenolsulphonethalein clearance were unremarkable. Higher doses of pitavastatin at shorter duration resulted in further exacerbation of renal toxicities, which suggests dose-dependency. Metabolism studies suggest that monkeys, more so than any other test species, form a greater proportion of 8-hydroxypitavastatin (active metabolite). While humans have a potential to form 8-hydroxypitavastatin, it was not considered a major human metabolite and was not measured in clinical studies. This metabolite is observed in monkey urine and feces. As a polar compound, 8-hydroxypitavastatin would be expected to be excreted in the urine along with the dihydroxypitavastatin and/or glucuronidated and excreted in the bile. A mechanistic study investigated a link between 8-hydroxypitavastatin and renal toxicity. In this study rats were administered 8-hydroxypitavastatin at 200 mg/kg BID for 2 weeks and 400 mg/kg/day BID for 1 week. All rats were found dead or sacrificed moribund before the study was scheduled for termination. Degeneration of the renal tubules, increased blood urea nitrogen and creatinine were also observed, suggesting a correlation. Fertility studies in rabbit showed mortality of treated males and females at 1 mg/kg/day (AUC=15,670 ng·h/ml, C_{max} =1184). Gross pathology (renal histopathology not performed) indicated whitening of kidneys, which may indicate ischemia, occurred at 100-fold clinical exposure at a 4 mg/day dose based on AUC. An explanation for the increased sensitivity of the rabbit to renal toxicity was not provided.

Thyroid toxicities

Pitavastatin increased thyroid follicular adenocarcinomas in male rats given ≥ 25 mg/kg/day in a lifetime carcinogenicity study (295-fold human exposure). This finding is attributed to excessive stimulation of thyroid follicular cells by elevated thyroid stimulating hormone (TSH). Pitavastatin appears to induce T₄ UDG-GT activity in liver which results in decreased plasma T₄ concentrations due to increased metabolism. Decreased T₄ leads to feedback-mediated increases in TSH release resulting in extensive follicular cell stimulation in the thyroid. This has been established for liver enzyme inducing agents, including statins. Follicular cell hypertrophy has been observed previously in subchronic toxicity testing. Also consistent with this hypothesis are potential mechanisms that address this finding. In short-term rat initiation/promotion studies designed to evaluate the follicular cell-promoting effect, this effect of pitavastatin was eliminated upon concomitant administration of T₄. This finding supports that idea that the thyroid follicular cell tumors observed at high doses are induced by increased plasma TSH concentrations due to negative feedback regulation due to induced hepatic T₄ metabolism. Rats are known to be particularly sensitive to this induced metabolism, because they lack T₄-binding globulin, which results in increased turnover of T₄ relative to other thyroid hormone species.

Hepatic toxicities

Hepatic effects have been seen in mice, rats and dogs. In a 1-month rat toxicity study, increases in transaminases (AST, ALT) were observed in females given 50 mg/kg/day (894-fold human exposure at 4 mg/day). Elevated transaminase levels were recoverable following drug withdrawal. In the chronic 6-month rat toxicity study no increases in transaminases were observed at the highest dose studied 10 mg/kg/day (56-fold human exposure at 4 mg/day dose). In the 3-month dog toxicity study an increase in ALT was seen at 3 mg/kg/day (24-fold human exposure at 4 mg/day dose). In the 12 month toxicity study both AST and ALT activity was increased in male dogs given 3 mg/kg/day (24-fold human exposure at 4 mg/day dose). Elevated transaminases were not detected upon recovery following drug withdrawal; however, hepatic histopathologies were not observed. In a 3-month dog toxicity study with pitavastatin at 10 mg/kg/day centrilobular dilatation of liver sinusoids were observed, which resolved during recovery. Increased centrilobular hepatocytes hypertrophy was observed in male mice given ≥ 12 mg/kg/day in the carcinogenicity study. A 3-month dog toxicity study with co-administration of mevalonic acid (100-150 mg/kg/day) and pitavastatin (5 mg/kg/day) resulted in an absence of transaminase elevations at doses up to 5 mg/kg/day (42-fold human exposure at 4 mg/day based on AUC). Studies in mice up to 225 mg/kg/day (150-fold human exposure based on AUC) did show the liver histopathology; however, pitavastatin does not appear to induce drug metabolizing enzymes, nor is it associated with the severe necrosis and cellular atypia and cholestasis observed in animals following treatment with other statins. Further support of a lessened biliary toxicity is seen in guinea pigs (3 mg/kg/day for 15 days) and hamsters (1 mg/kg/day for 14 days) where pitavastatin did not show any change in biliary lipids.

Skeletal muscle toxicities

Degeneration and necrosis were observed in the 1- and 3-month rat toxicity study at 50 mg/kg/day (894-fold human exposure at the 4 mg/day dose). Myopathy was not observed in the chronic rat study at doses up to 10 mg/kg/day (56-fold MHRD based on AUC). Myopathy was observed in the mouse carcinogenicity study at the highest dose (75 mg/kg/day) and in male rats given 25 mg/kg/day in the carcinogenicity study. Doses associated with myopathy in the lifetime carcinogenicity studies in mice and rats represent exposure levels 26 and 295-fold MRHD, respectively, based on AUC.

Lung toxicities

Pulmonary lesions were seen at 3 mg/kg/day (24-fold MRHD based on AUC) in the 3 month and 12-month dog toxicity studies. The Sponsor described these lesions as lipid, pneumonia-like, composed of foam and inflammatory cells. No other organ or species shows a similar lesion. This may be indicative of phospholipidosis, although transmission electron microscopy was not performed and it is uncertain if the lesions represented foamy macrophages that are the hallmark of phospholipidosis. Assessment in dogs given pitavastatin co-administered with mevalonic acid did not repeat the pulmonary findings suggesting an association with HMG-CoA reductase inhibition.

Forestomach toxicities

In mice and rats hyperkeratosis and acanthosis (hyperplasia) were observed with pitavastatin treatment. The thickening of the forestomach was not seen with subcutaneous administration, suggestive of a local, rather than systemic, effect. The Sponsor proposes a species-specific mechanism to explain this common finding in rodents given statins. Specifically, HMG-CoA reductase inhibition in keratinocytes of the mucosal epithelium of the forestomach results in decreased mevalonic acid and suppressed cholesterol synthesis by keratinocytes. This leads to an abnormal lipid composition in the presence of the statin, a result of accumulation of lipids in the junctional gaps of the keratinocyte layer. The results are structural changes at the mucosal epithelial surface of the forestomach, which may lead to detachment of keratin at the forestomach surface. Superficial cell proliferation, including basal cells of the epithelium, is induced to compensate for the detached keratin resulting in thickening of the mucosal epithelium through hyperplasia. Mevalonic acid has been shown to reverse this effect on the forestomach with other statins.

Testicular findings

Testicular changes (decreased testes weight, atrophy/degeneration of seminiferous tubules, impaired spermatocyte maturation and increased multinucleated giant cells) have been reported in dogs treated with statins. Histological changes in dog reproductive organs were not observed in the 12-month toxicity study at doses up to 3 mg/kg/day (>24-fold human systemic exposure at 4 mg/day dose) including sperm counts.

Metabolites and impurities

The principal circulating metabolites of pitavastatin in humans include the lactone, which the Sponsor considers pharmacologically inactive at the target, and small amounts of 8-hydroxypitavastatin which has pharmacologic activity slightly greater than that of the

parent pitavastatin based on *in vitro* HMG-CoA reductase inhibition assays. Studies performed with the lactone included single dose toxicology study in the dog were augmented by negative results in the *in vitro* genetic toxicology battery, a bacterial gene mutation and chromosomal aberration test. Repeat-dose studies with pitavastatin lactone at 0, 1, 3, 10 mg/kg/day and 10 mg/kg/day pitavastatin showed similar toxicology findings. The similarity in toxicity profile is not surprising; pitavastatin undergoes glucuronidation and subsequent hydrolysis to form pitavastatin lactone, and pitavastatin lactone can further hydrolyze to reform pitavastatin), *in vivo*. The NOAEL of the lactone was 1 mg/kg/day. Qualification of the 8-hydroxypitavastatin has been discussed under "renal toxicities".

Specific studies have been conducted on the 5-ketone metabolite of pitavastatin (M-3 metabolite) and the process impurities^{(b) (4)}

Specifications for these impurities have been set for these compounds as follows: (b) (4)

The total impurities specification for pitavastatin, excluding the (b) (4) The (b) (4) impurity was evaluated in single-dose oral toxicity study in mice where the toxicities observed were comparably to pitavastatin. Five studies were performed with a mixture of the (b) (4) including a single-dose study, a 1-month repeat-dose rat study, and an evaluation of potential genotoxicity using an *in vitro* battery (including Ames and chromosomal aberrations analyses) and an *in vivo* mouse micronucleus assay. The (b) (4) were considered to have a weaker toxicity potential than pitavastatin and a NOAEL of 50 mg/kg/day with 1-month dosing supports this. An equivocal positive response was seen in the chromosome aberration test at concentrations of ≥ 150 $\mu\text{g/ml}$, which were associated with significant cytotoxicity. Other genetic toxicology tests in the completed battery were negative, so based on a weight of evidence approach, the (b) (4) were considered not to have appreciable genotoxic potential. Similar toxicity studies were conducted in the rat with the (b) (4). The (b) (4) showed less toxicity than pitavastatin and did not show a genotoxic potential in the bacterial gene mutation or micronucleus assays. The chromosomal aberration test in Chinese hamster lung cells showed an increase in aberrations at the highest concentration tested; slight increases in chromosomal aberrations were noted in the direct plate method (as opposed to preincubation method) within 24 hours (with metabolic activation) at 300 $\mu\text{g/ml}$. The same concentration for 48 hours was too cytotoxic for evaluation. Weak increases were seen with preincubation, without metabolic activation at 750 $\mu\text{g/ml}$, and with metabolic activation at 600-825 $\mu\text{g/ml}$. Cytotoxicity was not measured in the preincubation protocol, but similar plates in parallel cultures indicated acceptable survival (50%) suggesting a valid study. This would suggest that the positive response occurred under conditions expected to cause significant cytotoxicity, which is very likely to be at significantly higher exposure levels than those achieved *in vivo* with pitavastatin.

Pitavastatin absorbs light in the 290-700 nm range with a minor peak at 328 and major peak at 245 nm. Specific studies to address phototoxicity were not performed. Tissue distribution studies in pigmented and non-pigmented rats did not indicate any particular affinity for skin or eyes in either strain. These studies, in addition to animal and clinical

studies, indicate that the likelihood of pitavastatin provoking phototoxic reactions is small.

Genetic Toxicology

Pitavastatin is not genotoxic, by weight of evidence. Pitavastatin was positive in a chromosomal aberration assay with metabolic activation in Chinese hamster lung (CHL) cells. The positive result was obtained at a concentration of pitavastatin that was close to that which caused 50% cytotoxicity with metabolic activation. Pitavastatin was negative for genotoxicity in a chromosomal aberration assay without metabolic activation in CHL cells. Pitavastatin was also negative in an Ames reverse mutation battery, *in vivo* mouse and rat micronucleus assays, an *in vivo/in vitro* single cell gel (Comet assay), and an *in vivo/in vitro* rat unscheduled DNA synthesis (UDS) assay.

Carcinogenicity

Initial carcinogenicity studies were performed prior to submission of the initial IND. In a 92-week mouse carcinogenicity study at doses of 1, 12, 30, 75 mg/kg/day of pitavastatin by oral gavage, survival was impaired in males by 37% and females by 47%. High incidences of liver and forestomach hypertrophy and hyperplasia and skeletal myofiber atrophy were observed. Executive Carcinogenicity Assessment Committee (ECAC) considered the dosing inadequate in males and requested further analysis to adjust for the excess deaths in the high dose group in the first year of the study as well as a peer review of the stomach histopathology to determine if the hyperplastic lesions may have progressed over time to a neoplastic response since carcinogenicity studies are typically 104 weeks duration.

In a 92-week rat carcinogenicity study at doses of 1, 5, 25 mg/kg/day by oral gavage, ECAC found the dose selection to be adequate. Survival in females at week 92 was 29%, 33%, 62%, 60% resulting in the early termination of the females. Male survival at week 104 was 35%, 38%, 38%, 56%. Survival in controls for each gender was similar to the lowest dose group. A high incidence of hypertrophy and hyperplasia of the liver and forestomach and skeletal myofiber atrophy were seen which might have progressed to neoplasia if the study were to have continued for the complete 104 week duration. An increased incidence of thyroid follicular cell adenocarcinomas was noted in males at 25 mg/kg/day. Pitavastatin increased thyroid follicular adenocarcinomas in male rats given ≥ 25 mg/kg/day in a lifetime carcinogenicity study (295-fold human exposure). This finding is attributed to excessive stimulation of thyroid follicular cells by elevated TSH. Pitavastatin appears to induce T₄ UDG-GT activity in male rat liver which results in decreased plasma T₄ based on increased metabolism. Decreased T₄ leads to a feedback-mediated increase in TSH release resulting in extensive follicular cell stimulation in the thyroid. This has been established for liver enzyme inducing agents, including statins. Rats are particularly sensitive to this induced metabolism because they lack T₄-binding globulin, which results in increased turnover of T₄ compared to other thyroid hormone species.

ECAC requested a transgenic mouse study to address these inadequacies. A 26-week carcinogenicity study was performed in Tg *rasH2* mice with administration of doses of

30, 75, 150 mg/kg pitavastatin by oral gavage. Males given 150 mg/kg/day had a higher frequency of alveolar/bronchiolar adenoma/carcinoma (2/25) and forestomach carcinoma (1/25). These tumors occurred at low frequency and are considered common tumors in Tg *rasH2* mice. This study was considered an adequate assessment of carcinogenicity by ECAC, without any statistically significant or clinically significant dose-related tumors.

A second Tg *rasH2* mouse carcinogenicity study was submitted using a 150 mg/kg/day pitavastatin dose with and without an initiating dose of urethane (250 mg/kg as a single IP dose on day 1) a known rodent carcinogen. Animals treated with urethane alone showed increased incidence of benign and malignant lung tumors that was unaffected by pitavastatin treatment. Thus, pitavastatin-treated animals did not show an increase in tumor incidence compared to urethane-treated controls. Urethane was used as an anesthetic during the carcinogenicity studies.

Overall, the carcinogenicity assessment suggests no tumorigenicity in rats at doses up to 25 mg/kg/day (295-fold human exposure at 4 mg/day based on AUC) after 104 weeks treatment and in Tg *rasH2* mice up to 150 mg/kg/day (194-fold human exposure at 4 mg/day based on AUC) after 26 weeks.

Pitavastatin lactone is not present in rodent plasma; however, rats liver microsomes produced significant amounts of pitavastatin lactone. Therefore, this metabolite has considered to have been tested in the 92-week rat carcinogenicity studies. Pitavastatin lactone was not genotoxic in an Ames assay with and without metabolic activation and was not genotoxic in a chromosomal aberration assay with and without metabolic activation.

Reproductive Toxicity – Fertility

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

Pitavastatin treatment in rabbits resulted in mortality in males and females administered 1 mg/kg/day (102-fold clinical systemic exposure) during a fertility study. Although the cause of death was not determined, rabbits had gross signs of renal toxicity (kidneys whitened), perhaps indicating ischemia. Lower doses (28-fold human systemic exposure) did not show significant toxicity in adult males and females. However decreased implantations, increased resorptions as well as decreased viable fetuses were observed.

Reproductive Toxicity – Pregnancy

Pitavastatin crosses the placental barrier into the fetus. Rat fetus concentrations were ≤36% of maternal plasma pitavastatin concentrations. Pitavastatin and 5-keto-pitavastatin are secreted by rats into milk at 7.2-fold greater pitavastatin levels than are present in maternal plasma. The predominant form of pitavastatin in the milk form is the unchanged parent molecule.

Embryo-fetal developmental studies were conducted in pregnant rats treated with 3, 10, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. Evidence of maternal toxicity was indicated by decreased body weight gain and decreased food consumption at the 30 mg/kg/day level. The maternal NOAEL was established at 10 mg/kg/day (82-fold human systemic exposure at 4 mg/day dose by AUC). A neonatal malformation of agnathia (absence/partial lower jaw) 1/347 neonates, and irregular alignment of caudal vertebrae 1/347 neonates was observed at this dose. The developmental NOAEL is established at 3 mg/kg/day (>25-fold 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 organogenesis. Body weight loss was seen at all doses (6.7-fold human systemic exposure at 4 mg/day dose based on AUC). At maternal doses ≥ 0.3 mg/kg/day mortality and spontaneous abortions were seen (28-fold human systemic exposure). Significant maternal liver and renal toxicity appears to have contributed to the toxicity. A skeletal variation of 27 presacral vertebrae was seen with 0.1 mg/kg/day litters.

In peri-postnatal studies in pregnant rats given oral gavage doses of pitavastatin at 1, 3, 10, 30 mg/kg/day from organogenesis through weaning, mortality was observed at 1 mg/kg/day. As a result of the maternal mortality an additional peri-postnatal study was performed in pregnant rats given oral gavage doses of pitavastatin at 0.1, 0.3 mg/kg/day from organogenesis through weaning. Insufficient lactation was noted at all doses which contributed to the decreased survival of the neonates in these dose groups. This occurs at 4-fold human systemic exposure at 4 mg/day dose based on AUC. Therefore, a developmental NOAEL could not be established even at the lowest dose tested of 0.1 mg/kg/day.

Unresolved toxicology issues (if any):

None.

Recommendations:

Approval (AP).

3 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

(b) (4)



Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ **Concurrence Yes** ___ **No** ___

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/s/

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concur w/AP recommendation

11/25/08

**45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

Submission date: October 1, 2008
Application number: NDA 22-363
Drug: Pitavistatin tablets
Application type: 505(b)(1), new molecular entity
Sponsor: Kowa Research Institute, Inc.

| ITEM | YES | NO | COMMENT |
|---|-----|----|--|
| 1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed? | X | | All files were submitted in eCTD format, and appear well organized. |
| 2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review? | X | | All files were submitted in eCTD format, and appear appropriately indexed, hyperlinked, and paginated to enable a timely and substantive review. |
| 3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)? | X | | All files were submitted in eCTD format, and appear legible so that a substantive review can be done. However, historical data for the pivotal 26-week Tg rasH2 mouse carcinogenicity study do not appear to have been included for review. Likewise, SAS export files do not appear to have been included for statistical review of tumor-related findings (Review issue only). |
| 4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA. (genotoxicity, reprotoxicity, adequate duration of chronic toxicity, carcinogenicity, etc.) | X | | A 6-month Tg rasH2 mouse carcinogenicity study was requested by executive CAC, because results of 92-week rodent carcinogenicity studies were potentially confounded due to shorter than optimal study duration. The results of this new pivotal study (and one new non-pivotal study of 2-stage carcinogenicity in lung of Tg rasH2 mice with and without coadministration of urethane) were included with the NDA submission. This study will be reviewed and submitted to executive CAC for concurrence. No pivotal studies appear to have been omitted from the NDA. |

| ITEM | YES | NO | COMMENT |
|--|-----|----|---|
| 5) Were the studies adequately designed (i.e., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)? | X | | Studies appear to be adequately designed. |
| 6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (i.e., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)? | X | | The sponsor is relying upon DMF(b) (4) for characterization of impurities and degradants found for pitavastatin, which include (b) (4). DMF (b) (4) provides data that indicate that these properties were highly similar between marketed and toxicology batches. The sponsor has submitted summarized batch analysis data independently of DMF(b) (4) to show that formulations used in non-clinical toxicology studies were within pre-defined specifications for stability. |
| 7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route? | X | | The route of administration used in pivotal animal studies was oral, and the intended route of exposure in humans is oral. |
| 8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels? | X | | The proposed draft label has been submitted, and it appears that the appropriate sections for the product were included and were generally in accordance with 21 CFR 201.577. Information is available to express human dose multiples in comparative serum/plasma AUC and C _{max} levels, where best applied. |

| ITEM | YES | NO | COMMENT |
|---|-----|----|---|
| 9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not. | X | | From a pharmacology/toxicology perspective, this NDA is fileable. |
| 10) Reasons for refusal to file: | | | |

Reviewing Pharmacologist/Supervisory Pharmacologist: C. Lee Elmore/Karen Davis-Bruno

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/s/

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11/21/2008 10:55:21 AM
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4/13/09

Executive CAC

Date of Meeting: April 7, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Al DeFelice, Ph.D., DCRP, Alternate Member
Karen Davis Bruno, Ph.D., DMEP, Pharm/Tox Supervisor
C. Lee Elmore, Ph.D., DMEP, Presenting Reviewer

Author of Draft: C. Lee Elmore, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 22-363

Drug Name: Livalo (pitavastatin tablets)

Sponsor: Kowa Research Institute, Inc.

Background: Kowa's initial IND submission included study reports for completed 92-week rat and mouse carcinogenicity studies. Dose selections in the 92 week mouse study were adequate in females, but were inadequate in males. High incidences of liver and forestomach hypertrophy and hyperplasia were observed. Survival adjusted analyses for neoplastic and non-neoplastic lesions were requested to correct for excess death in the high dose group during year 1, as was a peer review, blinded analysis of the stomach histopathology. Reinterpretation of existing histopathology data was deemed by ECAC as insufficient to determine if lesions would have progressed from hyperplasia to a neoplasia with longer duration of dosing. Rat dose selection was considered adequate following ECAC review. However, early termination of females at week 92 was problematic, because of the high incidence of liver and forestomach hypertrophy which may have progressed to neoplasia with longer duration dosing. The Exec CAC requested a transgenic mouse study to address lingering concerns from the original studies.

Tg *rasH2* Mouse Carcinogenicity Study: The sponsor submitted their protocol for a 26-week Tg *rasH2* mouse carcinogenicity study with data from a 4-week dose-finding study in CB6F1-Tg *rasH2* mice. The high-dose group of 250 mg/kg/day exceeded the MTD based on moderate/severe forestomach hyperplasia and inflammation (>30% incidence), without significant toxicity at 125 mg/kg/day. Doses of 30, 75, and 150 mg/kg/day were reviewed and considered appropriate by ECAC for the pivotal Tg *rasH2* mouse carcinogenicity study.

Pitavastatin was administered once-daily by oral gavage. The positive control was N-nitroso-N-methylurea, which produced the types and frequencies of tumors expected for this model. The vehicle control consisted of 0.5% carboxymethylcellulose in water. Tumors were observed at higher frequency than concurrent and laboratory historical controls in males given 150 mg/kg/day and included alveolar/bronchiolar

adenoma/carcinoma (2/25) and a forestomach carcinoma (1/25). However, these tumors were very low in frequency and are known to be common in Tg *rasH2* mice. Statistical evaluation did not show any significant increase in any tumors at any dose. Tumors were therefore considered not drug-related.

Executive CAC Recommendations and Conclusions:

- The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Exec CAC found that the study was negative for statistically significant drug related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DMEP

/Karen Davis-Bruno, Ph.D., Pharm/Tox Supervisor, DMEP

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/s/

David Jacobson-Kram
4/13/2009 08:40:59 AM