

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-275

OTHER REVIEW(S)

NDA 22-275
Samsca (tolvaptan)

Project Manager Overview (2nd cycle)
NDA 22-275 (hyponatremia)
SAMSCA (tolvaptan) 15, 30, and 60 mg Tablets
Pharmacologic Class: Vasopressin Antagonist

Overview:

Otsuka Pharmaceutical Co., Ltd. submitted a New Drug Application (NDA) for Samsca (tolvaptan) 15, 30 and 60 mg Tablets on October 23, 2007 (sponsor plans to market the 15 and 30 mg strength tablets at least initially). The indication is for treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Tolvaptan is a new molecular entity proposed for once daily oral administration. On June 25, 2008, the Cardiovascular and Renal Drugs Advisory Committee evaluated data on tolvaptan in support of treatment of euvolemic and hypervolemic hyponatremia. The AC members were asked to vote whether there was adequate evidence that tolvaptan can be expected to produce clinical benefits in the treatment of patients with hypervolemic or euvolemic hyponatremia. Several members of the AC said "yes", a few, however, said "no". The AC members unanimously agreed, however, that if tolvaptan is approved, that it be reserved for patients with *chronic* hyponatremia.

The Division reviewed this NDA under the Good Review Management Principles and Practices—the NDA served as DCRP's pilot GRMP application (aka: Review of the 21st Century) and received a Standard review. The Division sent the sponsor a complete response letter on August 22, 2008 citing the need for a REMS to ensure SAMSCA is initiated in the hospital setting, and the requirement that SAMSCA be dispensed with a medication guide. The sponsor's November 20, 2008 submission was considered the Class 2 complete response.

Class 2 Resubmission: Reviews and Memos

Office Director's Memo

Dr. Robert Temple; May 19, 2009

Decision: Approval (see memo for details)

OSE/DRISK Review of Risk Evaluation and Mitigation Strategy (REMS)

Gita Akhavan-Toyserkani, PharmD, MBA; May 19, 2009

In her review, Dr. Toyserkani recommended the following language be included in the approval letter:

- a) The REMS assessment plan should include but is not limited to the following: A survey of prescribers' and patient's understanding of the ██████████ risk of ODS ██████████
- b) A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c) A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective action to address noncompliance
- d) Narrative summary and analysis of cases of suspected ODS reported with use of Samsca.
- e) Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

b(4)

NOTE by D. Brum: Because no documented cases of ODS were observed in the sponsor's development program, bullet (a) above was corrected in the approval letter to read as follows:

A survey of prescribers' and patients' understanding of the risk of ODS.

NDA 22-275
Samsca (tolvaptan)

Dr. Temple agreed that the *revised* bullet should be incorporated in the action letter. Other minor edits were made to the last bullet, bullet (e).

DMEPA Review #2; April 8, 2009

Ms. Felicia Duffy

The Division for Medication Error Prevention and Analysis concluded SAMSCA does not appear to be vulnerable to name confusion that could lead to medication errors. On May 12, 2009, the Division sent comments to the sponsor regarding the proposed carton and container labeling. The sponsor revised the carton/container labeling and the Agency accepted the changes on 5/18/09.

Conclusion

An approval letter was signed by Dr. Temple on May 19, 2009 (PDUFA goal date May 20, 2009). The letter and enclosures includes the package insert with medication guide, carton and blister package labeling, the REMS, and a Dear Health Care Provider Letter and Prescriber Brochure (the latter two of which are REMS communication plan materials).

*Review by Daniel Brum, PharmD, MBA, RAC
May 20, 2009*

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/s/

Dan Brum
5/20/2009 06:49:29 AM
CSO

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Project Manager Overview
NDA 22-275 (hyponatremia)
SAMSCA (tolvaptan) 15, 30, and 60 mg Tablets
Pharmacologic Class: Vasopressin Antagonist

Overview:

Otsuka Pharmaceutical Co., Ltd. submitted a New Drug Application (NDA) for Samsca (tolvaptan) 15, 30 and 60 mg Tablets on October 23, 2007 (sponsor plans to market the 15 and 30 mg strength tablets at least initially). In the original labeling, the sponsor proposed to market SAMSCA for the treatment of euvolemic and hypervolemic hyponatremia and for the prevention of worsening hyponatremia. Subsequently, the proposed indication has been modified to treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Tolvaptan is a new molecular entity proposed for once daily oral administration. On June 25, 2008, the Cardiovascular and Renal Drugs Advisory Committee evaluated data on tolvaptan in support of treatment of euvolemic and hypervolemic hyponatremia. The AC members were asked to vote whether there was adequate evidence that tolvaptan can be expected to produce clinical benefits in the treatment of patients with chronic hypervolemic or euvolemic hyponatremia. Several members of the AC said "yes", a few, however, said "no". The AC members unanimously agreed, however, that if tolvaptan is approved, that it be reserved for patients with *chronic* hyponatremia.

The Division reviewed this NDA under the Good Review Management Principles and Practices—the NDA served as DCRP's pilot GRMP application (aka: Review of the 21st Century) and received a Standard review.

Original NDA Application Reviews

Office Director's Memo

Dr. Robert Temple; August 22, 2008

Decision: Complete response pending REMS approval.

Remarks: Does not recommend a contraindication in cirrhotics, however, warrants further discussion.

Division Director's Memo

Dr. Norman Stockbridge; August 22, 2008

Decision: Complete response.

Remarks: Requires acceptance of serum sodium as a valid surrogate because there is very little evidence of actual clinical benefit in the development program.

CDTL Memo

Dr. Ellis Unger; August 21, 2008

Decision: Complete response.

Remarks: Recommends a contraindication in cirrhotics and a REMS. Also, the safety database is only marginally adequate.

Clinical and Statistical Review (Combined); May 14, 2008

Dr. Aliza Thompson (hyponatremia)

Drs. Steve Bai and James Hung (Statistics)

Recommended Actions: Complete response (approvable for hyponatremia)

Hyponatremia: Efficacy

Tolvaptan's clinical development program for hyponatremia sought to establish the product's efficacy in raising serum sodium. The co-primary endpoints in the phase 3 hyponatremia trials were the AUC of the

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change from baseline in serum sodium up to days 4 and 30 following study drug initiation. Secondary endpoints largely addressed alternative ways of defining this change and tolvaptan's efficacy in raising serum sodium in sub-populations with greater or lesser degrees of hyponatremia. The results of these analyses are convincing that tolvaptan can raise serum sodium. The p-value for the primary endpoint was highly significant ($p < .0001$) in both phase 3 trials and secondary analyses in which changes in serum sodium were defined in other ways, supported the primary efficacy analysis and suggested that this finding was robust. But while these trials successfully establish tolvaptan's efficacy in raising serum sodium, the clinical significance of this rise in the studied population (subjects with a serum sodium < 135 mEq/L) is unclear.

Of the 15 listed secondary endpoints in the phase 3 hyponatremia trials, only one, the Short Form (SF)-12, addressed a possible clinical benefit to treatment beyond a change in a laboratory value. At day 30, a statistically significant improvement in the Mental Component Summary Score (MCSS) was seen in one of the phase 3 trials (156-02-235), while statistical significance was not reached in the other (156-03-238). Several concerns are raised by this instrument. These include statistical concerns due to the lack of a prespecified analysis plan and method for adjusting for multiplicity. In addition, it cannot be excluded that knowledge of changes in serum sodium may have biased a subject's response to questionnaire items ("my sodium is better therefore I am better"). The most critical issue, however, surrounds the validity of this instrument in the enrolled population. In a Study Endpoint Review, the Study Endpoints and Label Development Team deemed the SF-12 MCSS to be an inadequate measure of function and health related quality of life in the targeted population and recommended that it not be used to support efficacy claims. Thus the clinical significance of a change in serum sodium in this broadly defined population remains uncertain. That being said, in this reviewer's opinion, a change in serum sodium is a reasonable surrogate for clinical benefit in those with more severe hyponatremia.

Severe hyponatremia can cause morbidity and mortality and clinical benefit is likely to be incurred from interventions that raise serum sodium. Few subjects in tolvaptan's phase 3 studies had markedly low serum sodium levels, as these trials largely excluded symptomatic patients and those with "asymptomatic severe hyponatremia" that was "likely to require saline intervention." Nonetheless, analyses suggest that tolvaptan's ability to raise serum sodium levels was preserved in study subjects with the lowest baseline serum sodium levels. In this reviewer's opinion, tolvaptan is likely to raise serum sodium levels in patients with severe hyponatremia, a subpopulation of hyponatremic subjects in whom a change in serum sodium is expected to predict a clinically meaningful endpoint. A critical question that remains is how to define this level of "severe hyponatremia."

Historically, FDA has accepted a change in serum sodium as a surrogate endpoint. Conivaptan was approved for the treatment of euvolemic and hypovolemic hyponatremia by the Division of Metabolism and Endocrinology Products (DMEP) based on a change in serum sodium in subjects with a baseline serum sodium 115-130 mEq/L (in a double-blind, placebo-controlled trial cited on conivaptan's label, the mean serum sodium at entry was 123.3 mEq/L). During tolvaptan's development program, the need to enroll patients with "clinically significant hyponatremia" was repeatedly emphasized by DMEP and in defining this population, DMEP cited a serum sodium threshold of < 130 mEq/L. The basis for this cut-off is unclear and further discussion is needed on changes in serum sodium as a surrogate endpoint and the context(s) in which (and/or level of hyponatremia at which) a change in serum sodium can be expected to predict a clinically meaningful benefit. This issue will be addressed further at an Advisory Committee Meeting scheduled for late June.

Safety

Adequacy of the safety database

Although over 4,000 subjects were exposed to tolvaptan during its clinical development, the applicability of these data to the hyponatremic population at the doses proposed for use (15 to 60 mg) is uncertain. This is in part because the safety database is heavily weighted by subjects with heart failure who did not have hyponatremia and it is unclear if adverse effects observed in this population are predictive of adverse effects in subjects without heart failure or those with hyponatremia. Of the 3294 subjects with heart failure and/or hyponatremia treated in multiple-dose, placebo-controlled trials, only 607 subjects had a serum

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sodium <135 mEq/L, 189 subjects had a serum sodium <130 mEq/L and 52 subjects had a serum sodium <125 mEq/L. Moreover, the vast majority of subjects had heart failure; only 97 subjects carried a diagnosis of SIADH/other while 100 subjects were reported to have hyponatremia in the setting of cirrhosis. If susceptibility to tolvaptan's adverse effects is influenced by the underlying etiology of hyponatremia (cirrhosis, heart failure and SIADH/other) and/or baseline serum sodium level, analyses of this larger dataset may not provide an accurate assessment of tolvaptan's safety in these populations of interest.

This safety database also contains limited data on tolvaptan's safety at the upper end of the proposed dosage range for hyponatremia (60 mg), a dose that appears to be useful in getting hyponatremic patients to goal. Outside of the phase 3 hyponatremia trials, in which 223 subjects were exposed to tolvaptan doses of 15 to 60 mg, approximately 332 subjects with heart failure and/or hyponatremia and fewer than 70 subjects with hyponatremia were exposed to tolvaptan doses of 60 mg or greater in multiple dose-placebo controlled trials. For chronic use, the data are even more limited; at 6 months and beyond, all placebo-controlled data in hyponatremic subjects are derived from the phase 3 heart failure trial and hence reflect exposure to a 30 mg dose. Because of these limitations of the safety database and concerning safety signals in subjects with hyponatremia in the setting of cirrhosis and heart failure (discussed below), this reviewer believes that tolvaptan should not be approved for hyponatremia at this time.

Adverse events

The goal of treating hyponatremia is to raise serum sodium levels; however, overly rapid correction can lead to significant morbidity and mortality. Osmotic demyelination, characterized by dysarthria, dysphagia, paraparesis, quadraparesis, coma and seizures, has been reported with rapid rates of serum sodium correction, and, to minimize this risk, current guidelines recommend rates of correction of < 10-12 mEq/L over 24 hours. In tolvaptan's development program, no case of osmotic demyelination was reported and in the phase 3 hyponatremia studies, 5.3% of tolvaptan subjects had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 1.1% had an increase greater than 12 mEq/L at approximately 21 hours post first dose. In contrast, less than 1% of placebo-treated subjects had a rise greater than 8 mEq/L at approximately 8 hours and no placebo-treated subject had a rise greater than 12 mEq/L at approximately 21 hours post first dose. That being said, few subjects with marked hyponatremia were included in the phase 3 hyponatremia trials and it is unclear if the experience in the studied population is predictive of the risk of overly rapid correction in those with more severe hyponatremia. Analyses stratifying hyponatremic subjects by degree of hyponatremia (baseline serum sodium < 130 mEq/L vs. 130-134 mEq/L), suggest a greater risk of overly rapid (based on these guidelines) correction in tolvaptan-treated subjects with a lower baseline serum sodium. Because few subjects with marked hyponatremia were enrolled in these trials, the risk of overly rapid serum sodium correction in this key population remains poorly characterized. In this reviewer's opinion, if tolvaptan were approved for the treatment of hyponatremia, patients should be hospitalized for initiation and the label should advise clinicians of the need for frequent serum sodium measurements.

The hyponatremia safety dataset (N=607) was heavily weighted by heart failure subjects with hyponatremia enrolled in heart failure trials, and, as a result, safety analyses of this dataset to some extent mirrored those described below for the heart failure indication. A slightly greater incidence of cardiac arrest, dehydration, ventricular arrhythmia (ventricular fibrillation) was observed in tolvaptan-treated subjects. In addition, sepsis, ascites and respiratory failure were also reported at a slightly greater incidence in the tolvaptan arm. In all cases the absolute difference between treatment arms was less than 1.5%, though the relative difference was greater. To address possible unique risks, analyses were also stratified by underlying disease etiology (heart failure, cirrhosis and SIADH/other), and the discussion that follows addresses the safety findings in these subpopulations.

Hyponatremic subjects with heart failure: 410 subjects with both heart failure and hyponatremia were enrolled in multiple-dose, placebo-controlled trials. The majority of these subjects were enrolled in trials conducted for tolvaptan's proposed heart failure indication (as a treatment for worsening heart failure) and received a fixed 30 mg dose and not the proposed 15 to 60 mg dose-titration. The phase 3 heart failure trial enrolled the greatest number of subjects with both heart failure and hyponatremia and is the only placebo-controlled trial in which heart failure subjects with hyponatremia were exposed to tolvaptan for greater than 6 months. Of the 2,063 heart failure subjects treated with tolvaptan in the phase 3 heart failure trial, 242

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subjects had both heart failure and hyponatremia. Among all subjects enrolled in this trial, mortality was not greater in tolvaptan (N=2063) compared to placebo (N=2055) treated subjects with heart failure; however in the subgroup of subjects with both heart failure and hyponatremia, slightly greater mortality was observed in the tolvaptan (N=242) than the placebo (N=232) treatment arm. In this subgroup of subjects with both heart failure and hyponatremia, treatment-emergent fatalities were reported in 42.1% of tolvaptan and 38.4% of placebo-treated subjects. These results suggest that tolvaptan does not cause a dramatic increase in mortality in patients with both heart failure and hyponatremia; however, they do not exclude a small increase in mortality. In this reviewer's opinion, this potential risk outweighs the somewhat uncertain benefit of raising serum sodium with tolvaptan in patients with heart failure and hyponatremia.

Hyponatremic subjects with cirrhosis: Approximately 100 hyponatremic cirrhotics were studied in multiple-dose placebo-controlled trials; the majority of these subjects were enrolled in the phase 3 hyponatremia trials. Death rates were similar in tolvaptan and placebo-treated cirrhotics with hyponatremia. Analyses of adverse events, however, revealed a greater incidence of gastrointestinal (GI) bleeding in tolvaptan than placebo-treated cirrhotics with hyponatremia. In the phase 3 hyponatremia trials, in which subjects were exposed to 30 days of tolvaptan, GI bleeding was reported in 6 (9.5%) hyponatremic cirrhotics in the tolvaptan treatment arm and 1 (1.8%) hyponatremic cirrhotic in the placebo treatment arm. Pooling GI bleeding events with adverse event reports of hematomas and ecchymoses (another possible sign of impaired coagulation) magnified the difference in incidence between treatment arms. In the phase 3 hyponatremia trials, adverse event reports of GI bleeding, hematomas and/or ecchymoses were reported in 11 out of 63 (17.5%) hyponatremic cirrhotics treated with tolvaptan and only 1 out of 57 (1.8%) hyponatremic cirrhotics treated with placebo. The V2 receptor plays a role in von Willebrand factor release and hence a biologically plausible mechanism for this adverse effect in a population at high risk for bleeding can be hypothesized. That being said, the number of study subjects with hyponatremia and cirrhosis was small, as were the number of bleeding events reported. Nonetheless these data raise the question of an increased risk of bleeding in cirrhotics with hyponatremia treated with tolvaptan. In this reviewer's opinion, the safety database of cirrhotics with hyponatremia is insufficient to establish tolvaptan's safety at the doses proposed for use in cirrhotics with hyponatremia. Additional studies are needed to establish tolvaptan's safety in this population. Moreover, given the potential clinical importance of this safety signal, this reviewer believes that prior to approval, additional efficacy studies would need to establish tolvaptan's efficacy in hyponatremic subjects with cirrhosis via a clinically meaningful endpoint (an endpoint measuring how a patient feels, functions or survives) and not via a surrogate.

Hyponatremic subjects with SIADH/other: In contrast to the experience in subjects with hypervolemic hyponatremia, no unique concerning safety signals were identified in subjects with SIADH/other. Deaths, serious adverse events and severe adverse events all occurred at a numerically lower incidence in tolvaptan than placebo-treated subjects with SIADH/other. The safety data in subjects with SIADH/other do not suggest significant risks in this subgroup, however, few subjects with SIADH/other were studied; in multiple-dose, placebo-controlled trials, 97 subjects with SIADH/other were treated with tolvaptan. While the safety database containing all subjects with hyponatremia is larger, it is heavily weighted by heart failure subjects and subjects receiving a dose of 30 mg (less than the proposed upper end of the dosage range). It is unclear if the experience in subjects with heart failure and hyponatremia is predictive of risk in subjects with SIADH/other at the doses proposed for use. Moreover, this experience does not provide reassurance of safety; analyses do not exclude a small increase in mortality in tolvaptan-treated subjects with both heart failure and hyponatremia. In this reviewer's opinion, the safety database is too small to establish safety in this subpopulation at the doses proposed for use. Additional studies are needed to establish tolvaptan's safety in subjects with SIADH prior to approval for use in patients with euvolemic hyponatremia.

QT Studies; June 9, 2008

Interdisciplinary Review Team for QT Studies

This study was designed and conducted adequately to exclude a clinically significant QTc prolongation over the tolvaptan dose range studied. The largest upper limit of the two-sided 90% CI for the mean difference between tolvaptan (30-mg and 300-mg) and placebo was below 10 ms.

Clinical Pharmacology; June 9, 2008

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Drs. Peter Hinderling

Recommended action: Approval

Dose-response conclusion: Since a slow increase of serum sodium is a required feature of any dose regimen in hyponatremic patients, an increase of the dose of tolvaptan beyond 60 mg qd appears not to be an option. However, titration schemes for tolvaptan with bid administrations using asymmetrical doses and/or dose intervals could provide more constant levels of serum sodium throughout the dose interval. The sponsor did not explore this option even though the results of a Phase 2 study in CHF patients receiving daily doses of 30 mg either as 30 mg qd or 15 mg bid showed significantly greater morning trough values of serum sodium with the bid regimen than with the qd regimen.

Body weight conclusion: The results from the pivotal trial and the Phase 2 dose ranging study in hypervolemic CHF patients indicate that 30 mg tolvaptan qd [REDACTED]

[REDACTED] Administration of higher doses is necessary. Regimens with bid administration of tolvaptan using asymmetrical dose/and or time intervals may increase the safety of the required higher dose levels.

b(4)

Aquaresis conclusion: The aquaretic effect in healthy subjects reaches saturability at single doses ≥ 60 mg. In patients with hyponatremia or CHF higher doses may be required to reach a ceiling effect. It should be noted that a treatment with tolvaptan has two components: a first one triggered by the initial blockade of the V2-receptors and a second one that is triggered to counterbalance the thirst induced increase in water consumption caused by the first component. At the proposed therapeutic dose levels for the treatment of hyponatremia night time polyuria/pollakisuria may become a QOL concern if a long term treatment of hyponatremia is required. Polyuria would be a less of an issue in a short term effective treatment of worsening heart failure.

Deficiencies noted:

1. The quantitative aspects of the exposure-response-relationship including time course of the effect of tolvaptan and impact of a shorter than 24 h dose interval with both indications has not been performed adequately.
2. A substantial fraction of the circulating total radioactivity (about 40 %) has not been not identified. The unidentified metabolites could be pharmacologically active.
3. The sensitivity of the LC/MS/MS and HPLC/UV assays used is not sufficient for proper determination of λ_z and derived parameters for tolvaptan ($t_{1/2z}$, V_z/F , AUC_{∞}) and metabolites ($t_{1/2z}$ and AUC) at the proposed therapeutic dose levels.
4. The drug-drug interaction study with ketoconazole used 200 mg qd instead of the highest labeled dose of 400 mg qd. Therefore, the full inhibitory potential of ketoconazole on the exposure to tolvaptan remains unknown. In the drug interaction study with furosemide or hydrochlorothiazide a 30 mg dose of tolvaptan was used. A 60 mg dose of tolvaptan would have been more appropriate.
5. Evidence for the identity of the postulated metabolites DM-4129-4133 was not provided.

Pharmacometrics Review; June 9, 2008

Dr. Justin Earp

1. A clear increase is observed on serum sodium concentrations after treatment with tolvaptan when compared to placebo.

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2. Major covariates affecting pharmacokinetics are body weight, liver function (indicated by the Child-Pugh score) and disease status. Typical values of clearance were higher at 10 L/hr for individuals with hyponatremia when compared to patients with CHF (CL = 7 L/hr). Values for the volume of distribution were primarily dependent on liver impairment (1.5-fold increase) and proportional to body weight.
3. The individual responsiveness to tolvaptan was correlated with baseline serum sodium concentrations. At lower concentrations a greater response was observed and sufficient to return the patient to normal serum sodium concentrations within the studied patient population. For all baseline serum sodium levels observed in the studies, tolvaptan is generally effective in returning the serum sodium to between 135 and 145 mM.
4. No clear relationship between baseline renal function as indicated by creatinine clearance and effect on serum sodium concentrations was observed. Dose adjustment based on renal-impairment is not necessary.
5. There does not appear to be an increase in prolongation of the QT interval after tolvaptan administration at 5 times the maximum recommended therapeutic dose (60 mg).

Biopharmaceutics Review; June 30, 2008

Dr. Patrick Marroum

Dr. Marroum found the proposed dissolution method acceptable; however, the Q values of █████ in 60 minutes was not justified and should not be accepted. The dissolution method and specifications should be as follows:

USP apparatus 2

Rotation speed of 50 rpm

Medium: 900 ml of 0.22 SLS aqueous solution

Q: █████ in 30 minutes. This method is also acceptable in granting in vivo bioavailability waivers.

b(4)

Pharmacology Review; June 24, 2008

Dr. Xavier Joseph

Recommended action: Approval

In his review, Dr. Joseph makes several recommendations for changes to the labeling but has no recommendations for additional nonclinical studies.

Statistical Review of Carcinogenicity; February 7, 2008 and May 6, 2008

Drs. Atiar Rahman and Karl Lin

Based on the historical data, the combined incidences of liver cholangiocellular adenoma and carcinoma is considered to be a common type in male rats. Based on the adjustment method for multiple comparisons suggested by Lin and Rahman (see the original review for details), and the newly calculated exact p-value, the dose response relationship of the combined incidences of liver cholangiocellular adenoma and carcinoma in male rats is not considered to be statistically significant.

Chemistry Review #3; August 8, 2008

Dr. Amit Mitra

Recommended action: Approval

The Office of Compliance provided an "acceptable" recommendation.

Chemistry Review #2; July 28, 2008

Dr. Amit Mitra

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Recommended action: Approvable pending recommendation re: site inspections.

In his review, Dr. Mitra notes that Otsuka agreed to submit the validation report of [REDACTED] and consequent replacement of the dissolution test for the [REDACTED] as a supplement. Full validation data for the [REDACTED] method will also be included in the supplement. Otsuka committed to the task above within 2 months post-approval. His final recommendation was also pending a recommendation from Office of Compliance regarding the manufacturing sites.

b(4)

Chemistry Review #1; June 26, 2008

Dr. Amit Mitra

In his review, Dr. Mitra notes that several deficiencies were recorded in an Information Request letter sent to the sponsor and that satisfactory review of the requested information is required prior to approval of the NDA with respect to CMC. His final recommendation was also pending a recommendation from Office of Compliance regarding the manufacturing sites. Also, the sponsor requested categorical exclusion for their environmental assessment.

DMEPA Review

In a review dated July 18, 2008, the Division for Medication Error Prevention and Analysis found SAMSKA to be vulnerable [REDACTED]; however, the alternate name proposed, SAMSCA, does not appear to be vulnerable to name confusion that could lead to medication errors. If product approval is delayed beyond 90 days from July 18, 2008, the proposed name must be resubmitted for evaluation.

b(4)

DDMAC Review; June 12, 2008

DDMAC provided comments on the sponsor's proposed package insert.

SEALD Labeling Review; July 31, 2008

SEALD Endpoints Review; July 17, 2008 (hyponatremia)

The review concludes that neither the SF-12 or Hyponatremia Disease Specific Survey (HDS) represent meaningful, comprehensive, appropriate, and interpretable measurements of the symptoms of hyponatremia or HRQL for the target population. Therefore, the instruments cannot be used as stand-alone measures of treatment benefit for efficacy claims.

[REDACTED]

b(4)

SEALD Endpoints Review; April 15, 2008 (hyponatremia)

The review concludes that the SF-12 PCS and MCS are not adequate measurements of function and health-related quality of life as proposed and cannot be utilized to support efficacy claims.

[REDACTED]

PeRC Meeting; August 13, 2008

b(4)

1. Ensure the indication identifies use in chronic hyponatremia (and to avoid use in acute hyponatremia).
2. The sponsor's pediatric proposal (PPSR) in kids aged 6-17 needs to be modified to mirror patients as specified in the labeling. The current proposal includes "acute or chronic" and "serum sodium < 135 mEq/L".
3. A waiver in kids aged 0-5 is acceptable based on the proposed labeling.

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DSI Reports; August 6, 2008; August 4, 2008 (VAI); May 1, 2008 (VAI); April 7, 2008 (VAI); April 3, 2008 (NAI)

The August 6, 2008 review concludes that while 6 of 7 clinical investigators inspected were issued Form FDA 483 inspection observations, it does not appear that the compliance deviations would significantly alter overall study outcome.

Actions:

A complete response letter was drafted for Dr. Temple's signature.

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this page is the manifestation of the electronic signature.**

/s/

Dan Brum
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CSO