

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-275

SUMMARY REVIEW



**DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS
Cross-Discipline Team Leader (CDTL) Review**

Date: August 20, 2008

NDA: 22-275
Samsca (tolvaptan) tablets, 15, 30, and 60 mg
Otsuka Pharmaceutical
Treatment of hypervolemic and euvolemic hyponatremia

Status: Standard

Submitted: 23 October 2007

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Reviewer: Ellis F. Unger, M.D.
Deputy Director
Division of Cardiovascular and Renal Products

Through: Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products

To: The File

This secondary review is based, in part, on the primary reviews of:

- Chemistry (Amit K. Mitra), June 27, 2008
- Preclinical Pharmacology and Toxicology (Xavier Joseph, Charles A. Resnick), June 24, 2008
- Clinical Pharmacology and Biopharmaceutics, (Peter H. Hinderling, Justin Earp, Patrick J. Marroum, Yaning Wang), June 9, 2008
- QT (Joanne Zhang, Jingyu Luan, Suchitra Balakrishnan, Rajnikanth Madabushi, Christine Garnett), April 2, 2008
- Clinical and Statistical (Aliza Thompson, Steven Bai, James Hung), May 14, 2008
- Study Endpoints and Label Development (Ann Marie Trentacosti), February 12, 2008

The legal basis for submission is 505(b)(1).

NOTE: The sponsor originally submitted a NDA 22-275 to cover [REDACTED]
[REDACTED] a hyponatremia indication.

1) NDA 22-275 is the application in support of treatment of patients with
hypervolemic and euvolemic hyponatremia; [REDACTED]

[REDACTED] This
document is the Cross-Discipline Team Leader's (CDTL) Review for the hyponatremia
indication, NDA 22-275. [REDACTED]

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1. Introduction

Requested indication for Tolvaptan:

Tolvaptan is indicated for the treatment of hypervolemic and euvolemic hyponatremia (including patients with heart failure, cirrhosis, SIADH, etc) and for the prevention of hyponatremia. The proposed initial dose regimen for the treatment of hyponatremia is 15 mg tolvaptan qd. The dose may be increased to 30 mg at intervals of at least 24 h, and to a maximum of 60 mg/day as tolerated to achieve the desired level of serum sodium. During titration the patients should be monitored for serum sodium and volume status.

Mode of Action:

Tolvaptan [\pm -4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl) carbonyl]-o-toluidide] is racemic and has a MW of 448.9. It is a non-peptide, selective vasopressin V₂ receptor antagonist with an affinity for the V₂ receptor that is 1.8 times that of the native arginine vasopressin (AVP). AVP is a neuropeptide synthesized in the para-ventricular and supra-optic nuclei of the hypothalamus, transported to the posterior pituitary gland and released into the general circulation. A decrease in volume or pressure leads to an increase in circulating AVP and an increase in osmolality. Stimulation of the V₂ receptors by AVP leads to synthesis and insertion of aquaporin-2 water channels in the collecting duct cells of the kidney, allowing water re-absorption and antidiuresis. However, with blockade of the receptor, there is a counter-regulatory increase in AVP levels, leading to increased thirst and increased fluid ingestion. Thus, the net reduction in extra-cellular volume is significantly smaller than the increase in urine volume. Serum potassium concentrations and urinary excretion of sodium and potassium do not appear to be affected significantly.

Conivaptan, a V_{1a}/V₂ receptor antagonist, is the first agent in this pharmacological class and is approved for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients. In contrast to tolvaptan which is administered by the oral route, conivaptan's mode of administration is by intravenous injection.

Drug Substance and Drug Product:

The sponsor used the clinical service formulations of strength 15, 30 and 60 mg in the phase 2 and 3 clinical trials. The sponsor proposes to market only the 15 and 30 mg tablets. The sponsor has not demonstrated *in vivo* bioequivalence of the clinical service formulations and the commercial formulations. The clinical service and to-be-marketed formulations of 30 mg strength are compositionally identical. The respective formulations of 15 mg strength are compositionally different. The sponsor has demonstrated that the 15 mg and 30 mg clinical service formulations are bioequivalent and seeks granting of a biowaiver based on *in vitro* dissolution data.

The drug substance exhibits low and pH independent water solubility. Tolvaptan can be classified preliminarily as a BCS IV drug.

2. Background

Tolvaptan has not been approved by any regulatory authority to date. The drug is an orally administered selective vasopressin V₂ receptor antagonist developed for the treatment of [redacted] euvolemic and hypervolemic hyponatremia (NDA 22-275). Tolvaptan is a member of a relatively new chemical and pharmacologic class of drugs known as "vaptans" or aquaretics. These drugs block the vasopressin V₂ receptor located on the basolateral aspect of collecting duct cells of the renal tubule, thereby lowering urine osmolality, inducing a water diuresis (aquaresis), and raising serum osmolality and sodium concentrations.

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To date, conivaptan is the only member of this class approved for use in the United States. Relative to conivaptan, however, tolvaptan presents important new risks, because conivaptan is an intravenous drug that is approved only for use for 4 days in hospitalized patients. Thus, whereas monitoring is presumably intense for an IV drug such as conivaptan, there is the strong potential for tolvaptan to be used casually in an outpatient setting, with only limited monitoring.

Another member of this class, mozavaptan, is approved for use in Japan. To date, no members of this class have been approved in the United States for chronic use in the treatment of hyponatremia.

Tolvaptan is formulated in 15 and 30 mg tablets. For the indication of hypervolemic and euvolemic hyponatremia, 15 mg tolvaptan is to be taken by mouth once a day with dose titration to 30 mg, and then to a maximum dose of 60 mg once a day, as needed for effect.

3. CMC/Device

Drug Substance

Tolvaptan drug substance is a new molecular entity that is synthesized as a [redacted] in a racemic form. Tolvaptan has an asymmetric center and can exist as two enantiomers. The drug substance is a racemate and exhibits no optical rotation. The sponsor characterized each optical isomer separately. Tolvaptan drug substance is [redacted]

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[redacted] This is a complex manufacturing process, and a number of deficiencies were raised by the CMC Review Team. These were communicated to the sponsor in an Information Request Letter, and adequately addressed, with the exception of issue #1, below. The sponsor is planning to address this concern as a post-marketing agreement, and the CMC Team has agreed with this approach (see below).

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Drug Product

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There are compositional differences between the tablets used the clinical trials and the proposed to-be-marketed drug product.

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The applicant has compared the dissolution profiles of the to-be-marketed 30 mg tablet and the 30 mg tablet used in clinical development, and they are identical. Similarly, the dissolution profile for 2 x 15 mg tablets is super-imposable to that of the 30 mg tablet, and the dissolution profiles for the proposed commercial 15, 30, and 60 mg tablets are similar. Based on similar dissolution, the sponsor requested a biowaiver for the proposed commercial formula. OCP was consulted to review the bio-waiver. OCP requested additional information on the dissolution method, and based on the additional data received, the biowaiver was granted.

Impurity Profile

The sponsor has categorized the drug related impurities into five categories: 1) starting material; 2) intermediates; 3) degradation products; 4) byproducts derived from impurities in starting materials; 5) byproducts stability and shelf-life derived from side reaction. The sponsor provided the route of formation of the impurities, and provided the impurity profiles of all drug substance batches manufactured since the early development. Toluene sulfonic acid is released during the manufacturing process, and the final step of the synthetic process involves recrystallization in _____. Therefore, under experimental conditions it is possible to form toluene sulfonic acid methyl ester (a potential genotoxic carcinogen). Toluene sulfonic acid methyl ester had not been listed as a drug-related impurity, and the sponsor was requested to determine residual amount of the impurity and to adopt a specification for it.

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Subsequently, the sponsor demonstrated that levels of residual methyl ester of toluene sulfonic acid are not more than _____ in all batches, which is below the currently accepted threshold for toxicological concern at the maximum daily dose of the drug. Therefore, the sponsor claimed that adoption of an acceptance criterion for residual methyl ester of toluene sulfonic acid is unnecessary. The CMC team agreed with the sponsor's claim.

Stability Data

Stability studies indicated that the drug substance is stable under extreme conditions. The 2-year long-term and 6-month accelerated stability data on three production batches were acceptable. The sponsor requested a retest period _____ and this request can be granted. The stability data for the proposed commercial tablets were generated under room temperature and accelerated conditions. Based on the satisfactory stability data for the 15 and 30 mg tablets, a tentative shelf life of 36 months can be granted. For the 60 mg strength tablets, a shelf-life of 24 months was requested by the sponsor and may be granted.

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Facilities Review/Inspection

All facilities inspections have been completed and the Offices of Compliance and New Drug Quality Assessment have determined that these facilities are acceptable.

The CMC Team initially made an "Approvable" recommendation for the NDA, noting several deficiencies in the application. These were transmitted to the sponsor in an Information Request Letter. Pursuant to their response, all issues have been addressed, with the sponsor's acceptance of one post-approval agreement:

Within 2 months of approval, "Otsuka agrees to submit the validation report of _____ consequent replacement of the dissolution test for the _____ as a supplement. Full validation data for the _____ method will also be included in the supplement."

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4. Nonclinical Pharmacology/Toxicology

- Pharmacodynamic Activities

Tolvaptan competitively blocks the binding of arginine vasopressin (AVP) to V_2 receptors, inhibiting AVP-induced water reabsorption at the renal collecting ducts, thereby increasing free water excretion. There are no differences in human V_2 and V_{1a} receptor antagonism between tolvaptan's 2 optical isomers [(R)-(+)-OPC-41061 and (S)-(-)-OPC-41061] and its racemic form. The metabolites of tolvaptan showed no activity at human V_2 and V_{1a} receptors or weak antagonistic activity compared to tolvaptan. Neither optical isomers nor metabolites of tolvaptan showed any antagonistic activity at human V_{1b} receptors.

In both intact animals and animal models of hyponatremia, tolvaptan dose-dependently increased urine volume, decreased urine osmolality, increased free water clearance, and increased serum sodium concentration.

The effects of tolvaptan on hemodynamics and renal function were evaluated in sedated conscious dogs in a model of pacing-induced heart failure. A single 10 mg/kg oral tolvaptan dose increased water clearance and serum sodium concentration, accompanied by a decrease in cardiac preload, suggesting that tolvaptan may be useful for volume overload heart failure.

Although tolvaptan has greater affinity for the V_2 receptor, it exhibits weak effects on the V_{1a} receptor. Tolvaptan inhibited AVP-induced platelet aggregation (which is mediated via V_{1a} receptors), but not adenosine diphosphate (ADP)-induced platelet aggregation, confirming its action as a V_{1a} receptor antagonist, and suggesting that the drug could alter platelet function.

In safety pharmacology studies, neither tolvaptan nor its metabolites exhibited important effects on the nervous, respiratory, cardiovascular, or gastrointestinal systems.

- Pharmacokinetics and Metabolism

In animal studies, C_{max} and AUC were dose-dependent, T_{max} ranged from 2 to 4 hours, and the elimination half-life ranged from 4.4 to 6.4 hours. The volume of distribution was substantially greater than total body water, suggesting extensive extravascular distribution and/or preferential binding to tissue proteins.

Tolvaptan and its major human metabolites, DM-4103 and DM-4107, bind extensively to plasma proteins (97.2% or higher) as determined by the ultrafiltration method. The extent of binding was independent of drug concentration. In distribution studies of radiolabeled tolvaptan, activity was higher in liver, stomach, small intestine, kidneys, and adrenal glands than in serum. Radioactivity in the central nervous system was low.

Tolvaptan's overall biotransformation profile was similar across different animal species and humans. Tolvaptan is metabolized primarily by 3 major pathways: hydroxylation to form DM-4110, DM-4111 and DM-4119; dehydrogenation to form MOP-21826; deamidation to form DM-4128; and hydroxylation after cleavage of the benzazepine ring to form DM-4104. MOP-21826 is further converted to DM-4105 and DM-4103. DM-4104 is further converted to DM-4107.

CYP3A4 is responsible for catalyzing the primary metabolic reactions; CYP1A1 catalyzes deamidation to DM-4128. Other CYP isoforms are not involved in tolvaptan's metabolism. At clinically relevant concentrations, tolvaptan did not inhibit CYP isoforms *in vitro* or induce the drug metabolizing enzymes *in vivo*. Following oral administration of radiolabeled tolvaptan to rats and dogs, most of the radioactivity was recovered in the feces.

- Toxicology Findings

Toxicity studies were performed using the  formulation of tolvaptan, the formulation used for clinical trials and intended for marketing.

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The only treatment-related adverse effects observed in a 52-week oral canine toxicity study (30, 100 and 1000 mg/kg/day) were reduced adrenocorticocyte vacuolation and/or increased cortical width in the adrenal glands of mid- and high-dose animals, attributed to the physiological adaptive response to the stress of chronic marked diuresis. A NOAEL was not established for the adrenocortical findings in dogs since increased cortical width was also noted at the low dose (30 mg/kg/day) in a supplementary dog study.

In a 26-week study in rats (30, 100 and 1000 mg/kg/day), there were deaths in the high-dose female group after the first few doses of tolvaptan, attributed to increased urine output and dehydration. After additional water was made available to the animals, there were no additional deaths. Increases in water consumption and urine volume and decreases in urine specific gravity and osmolality were observed throughout the study. The NOAELs were 1000 mg/kg/day for males and 100 mg/kg/day for females. In a 4-week oral toxicity study in rats, prothrombin time (PT) and activated partial thromboplastin time (APTT) were prolonged at doses of ≥ 300 mg/kg/day, attributed to depletion of vitamin K-dependent coagulation factors. A mechanistic study in rats showed that the prolongation of PT and APTT occurred only under fasting conditions and was reversed by vitamin K supplementation.

- Carcinogenicity

Two years of oral administration of tolvaptan (100, 300 and 1000 mg/kg/day in males and 30, 100, 300 and 1000 mg/kg/day in females) did not increase the incidence of tumors in the rat. The highest dose employed in that study was about 160 times the maximum recommended human dose (MRHD) of 60 mg/day on a mg/m^2 basis. In the mouse, two years of oral administration of tolvaptan (10, 30 and 60 mg/kg/day in males and 10, 30 and 100 mg/kg/day in females) also did not produce an increased incidence of tumors. The highest doses employed in male and female mice were about 5 and 8 times the MRHD, respectively, on a mg/m^2 basis.

- Reproductive Toxicology

In a fertility study in rats, oral administration of tolvaptan (100, 300, and 1000 mg/kg/day) was associated with reductions in weight gain and food consumption in both sexes. Numbers of

corpora lutea and implants at 1000 mg/kg/day were significantly lower than control. The drug treatment did not result in any grossly observable fetal abnormalities. Oral administration of tolvaptan to pregnant rats during organogenesis was associated with dose-related reductions in food consumption and weight gain, reduced fetal weight and delayed fetal ossification. Oral administration of tolvaptan to pregnant rabbits was associated with dose-related maternal toxicity (reduction in food consumption and weight gain at all doses, and abortion at mid and high doses). At 1000 mg/kg/day, there were increased incidences of post-implantation loss, fetal microphthalmia, open eyelids, cleft palate, brachymelia, and skeletal malformations. Lower doses did not produce any adverse fetal effects. Rats dosed with tolvaptan (10, 100 and 1000 mg/kg/day) from day 7 of gestation through day 21 postpartum experienced reductions in food consumption (≥ 10 mg/kg/day) and maternal weight gain (100 and 1000 mg/kg/day). One dam died at the high dose. Increased perinatal death and suppressed body weight gain of offspring were noted at this same dosage level. F0 maternal drug treatment at doses up to 1000 mg/kg/day had no significant effect on the physical development, reflex functions, learning ability or reproductive performance of the F1 progeny.

Tolvaptan tested negative in *in vitro* and *in vivo* test systems (bacterial reverse mutation assay and chromosomal aberration test in Chinese hamster lung fibroblast cells; micronucleus assay in rat bone marrow erythrocytes).

Single dose toxicity studies (rats) and *in vitro* genotoxicity studies with DM-4103 and DM-4107, the major human metabolites of tolvaptan, revealed no notable toxicity or genotoxic potential.

Tolvaptan-derived radioactivity was distributed to the fetal tissues in pregnant rats and secreted in the milk of lactating rats, suggesting potential fetal and neonatal exposure if administered to pregnant or lactating women.

- Summary of Nonclinical Safety Issues Relevant to Clinical Use

Chronic toxicity studies conducted in both rats and dogs did not reveal any notable toxicity in either species. Prolongation of PT and APTT observed in rat studies were thought to be due to depletion of vitamin K-dependent clotting factors, and were not observed in the dog. Tolvaptan inhibited AVP-induced platelet aggregation, suggesting that the drug could predispose to bleeding by altering platelet function as well. Dose limiting clinical signs (dehydration and reduced food consumption and body weight) observed in female rats and male and female dogs at 1000 mg/kg/day were considered to be the consequence of an exaggerated pharmacologic action of the drug. Nonclinical studies have shown no genotoxic or carcinogenic potential. The apparent drug-related effects on fertility and embryo/fetal development in rats and rabbits occurred at relatively high doses (about 160 times the MRHD on a mg/m² basis in rats and 324 times the MRHD in rabbits), and may have been secondary to maternal toxicity at these doses. The review team did not consider the reproductive toxicity findings observed at the very high multiples of the MRHD to constitute an approvability issue. However, since tolvaptan was shown to be secreted in the milk of lactating rats, they recommended (for labeling) that women receiving tolvaptan should not breast feed.

The Pharmacology-Toxicology review team did not identify any approvability issues for tolvaptan.

5. Clinical Pharmacology/Biopharmaceutics

“From a Clinical Pharmacology viewpoint the submission is acceptable.”

- General Clinical Pharmacology Considerations, Absorption, Metabolism, Half-Life, Food Effects, Bioavailability, and Elimination

In healthy subjects, single tolvaptan doses of up to 480 mg and multiple doses up to 300 mg exhibit dose-proportional kinetics. Maximum plasma concentrations of tolvaptan are attained at a T_{max} of 2 to 4 hours. At doses ≥ 60 mg, the increase in C_{max} is less than dose-proportional. Tolvaptan's pharmacokinetics are stereospecific; the steady-state ratio of S(-) to R(+) enantiomers is approximately 3.

At least 40% of an oral dose of tolvaptan is absorbed as tolvaptan or metabolites. Food has no impact on the bioavailability of tolvaptan. *In vitro* data demonstrate that tolvaptan is both a substrate and inhibitor of MDR1; tolvaptan is metabolized mainly by CYP3A. Tolvaptan is highly plasma protein bound ($\geq 0.99\%$) and distributed in an apparent volume of distribution of 4.8 L/kg. Tolvaptan is eliminated entirely by non-renal routes.

Mean oral clearance is 4 mL/min/kg and the mean apparent terminal $t_{1/2}$ is 12 hours; however, the dominant $t_{1/2}$ is shorter. Oral clearance increases with increasing body weight, but neither age nor sex affects clearance independently. When given every 24 hours, the accumulation factor is 1.4. At steady state, the trough concentration is $<20\%$ of the peak concentration. Tolvaptan's metabolites do not exhibit relevant V_2 -receptor antagonism.

In patients with moderate and severe hepatic impairment, the clearance of tolvaptan is reduced by about 20% and the volume of distribution increased by about 50%. CHF decreases clearance by 30%, but the reviewing team did not feel that dose adjustment is needed. Mild, moderate, and severe renal impairment do not increase exposure to tolvaptan. The dialyzability of tolvaptan has not been determined.

In summary, the major covariates affecting tolvaptan's pharmacokinetics are body weight, liver function (indicated by the Child-Pugh score) and disease status. Volume of distribution was primarily dependent on liver impairment (1.5-fold increase) and proportional to body weight. Elimination is not affected by even severe renal impairment, and dose adjustment based on renal status is not necessary.

- Drug-Drug Interactions

Pharmacokinetics: Ketoconazole (200 mg qd) increases peak and average exposure to tolvaptan by a factor of 5, and it is likely that the highest labeled dose of ketoconazole (400 mg qd) would increase exposure even more, but this was not assessed. Rifampin reduces exposure to tolvaptan by 85%. Co-administration of lovastatin, digoxin, hydrochlorothiazide, and furosemide do not affect exposure to tolvaptan. The review team noted, however, that a 30 mg tolvaptan dose was used in the drug interaction study with furosemide or hydrochlorothiazide. A 60 mg dose of tolvaptan would have been more appropriate and informative.

Tolvaptan does not impact the pharmacokinetics of co-administered warfarin. Tolvaptan increases the exposure to digoxin and lovastatin 1.3-fold and 1.4-fold, respectively. Tolvaptan does not affect the exposure to amiodarone, hydrochlorothiazide, or furosemide.

Pharmacodynamics: Co-administration of tolvaptan with warfarin does not affect APTT, PT, or the international normalized ratio (INR). When furosemide or hydrochlorothiazide are co-administered with tolvaptan, the aquaretic effect is not enhanced compared to administration of tolvaptan alone. However, co-administration of tolvaptan with furosemide or hydrochlorothiazide enhances the effect of the diuretics.

Reviewer's comments: Digoxin is a MDR1 substrate and tolvaptan is a substrate and an inhibitor of this transporter. Measurements of digoxin renal clearance suggest that tolvaptan has a greater effect on digoxin pharmacokinetics than indicated by the reported AUC and C_{max} measurements. Digoxin has a narrow therapeutic window and the label should alert clinicians to the possibility of increases in digoxin levels in patients on tolvaptan.

- Drug-Other Interactions

Grapefruit juice increases peak and average exposure to tolvaptan by a factor of 1.8, and this information seems appropriate for labeling. The submission does not contain any additional information on the possible impact of herbal products, diet, smoking or alcohol use on exposure or response. No dose recommendations can be made regarding these extrinsic factors.

- Gender, Age, Other Demographic Characteristics, Baseline Disease Status

No dose adjustment is recommended for the elderly, females versus males, race other than Caucasian, patients with mild, moderate or severe liver impairment, or patients with mild to severe renal impairment. The predicted increases in exposure are not of sufficient magnitude to affect safety.

No recommendations can be made for pediatric patients, because the pharmacokinetics of tolvaptan have not been investigated in this population.

- Pharmacodynamics

In healthy subjects, single doses of tolvaptan between 60 and 480 mg exhibited a rapid onset of action, within 2-4 hours post-dose. Peak increases in serum sodium concentration from 4.6 to 7.8 mEq/L were observed between 6-12 hours post-dose, demonstrating that changes in serum sodium lagged behind the tolvaptan plasma concentrations. Not surprisingly, changes in serum sodium concentration persist after aquaresis has subsided. More than 60% of the peak effect on serum sodium concentration was sustained at trough, despite the fact that urine output was no longer enhanced.

Peak urinary excretion rates of 8.5 to 10 mL/min were attained over a range of doses differing by factor of 8, suggesting saturability of the aquaretic effect. Consistent with the saturable aquaretic effect, single tolvaptan doses in excess of 60 mg appeared to have little additional effect on sodium concentrations. Thus, the data support the proposed upper dose limit of 60 mg in patients with hyponatremia.

The review team noted that individual responsiveness to tolvaptan was correlated with baseline serum sodium concentrations: at lower concentrations a greater response was observed,

sufficient to return the patient to normal serum sodium range. They noted that for all baseline serum sodium levels observed in the studies, tolvaptan was generally effective in returning the serum sodium to between 135 and 145 mM.

Reviewer's Comments: This reviewer notes that the tolvaptan dose was titrated to effect in these studies. Thus, subjects with lower baseline serum sodium concentrations were not necessarily *more responsive* than subjects with higher baseline concentrations. In fact, they did *respond*, but they may have received more intensive tolvaptan treatment (higher doses or more prolonged treatment).

The results of a Phase 2 study in CHF comparing BID to QD dosing demonstrated that subjects who received 15 mg bid experienced significantly greater morning trough serum sodium concentrations than subjects who received 30 mg QD; however, the sponsor did not pursue further BID dosing.

In hypervolemic CHF patients and patients with hyponatremia secondary to liver disease, the onset of tolvaptan's aquaretic effect was rapid. Peak aquaretic effects were observed 6 hours post-dose and the effect size was dose-related. Tolvaptan's aquaretic effect appeared to be greater in subjects with hyponatremia secondary to liver disease than in those with hypervolemic CHF. In the former group, polyuria continued 12-24 hours post-dose.

At all doses tested, tolvaptan did not importantly affect serum potassium concentration.

- Thorough QT study or other QT assessment

The study was designed and conducted adequately to exclude clinically significant QTc prolongation over the tolvaptan dose range studied.

The Thorough QT Study was a double-blind (for tolvaptan and placebo), placebo- and positive-controlled, multiple dose, parallel-arm study, that evaluated two dose regimens of tolvaptan (30 mg and 300 mg) on QTcF interval, and compared them with placebo. The greatest QT effect associated with tolvaptan was observed on Day 5 in subjects who had received the suprathreshold dose of 300 mg QD X5 days. Under these circumstances, tolvaptan plasma concentrations were 4.5-fold higher than peak concentrations following the 30-mg dose, and 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 ($\Delta\Delta\text{QTcI} = 4.6$ ms, 90% C.I. 0.1, 9.1 ms). There was no relationship between the tolvaptan plasma concentration and $\Delta\Delta\text{QTcF}$ interval. The 300-mg dose covers the expected increase in tolvaptan concentrations due to the known intrinsic and extrinsic factors.

Moxifloxacin increased the $\Delta\Delta\text{QTcI}$ interval by 12 ms at 2 hours after dosing on Day 1, and 17 ms at 1 hour after dosing on Day 5. Thus, the study demonstrated assay sensitivity, in that the results show that the study was adequately designed and conducted to detect an effect on the QT interval if in fact one had been present.

In summary, tolvaptan does not prolong the QT interval at 300 mg QD, a dose that is 5 times the maximum recommended therapeutic dose (60 mg).

- Deficiencies

The Clinical Pharmacology review team noted the following deficiency with the potential to impact safety and trigger a post-marketing requirement:

1. 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.

Reviewer's Comments: In addition, since 200 mg ketoconazole increased exposure by a factor of 5, and the thorough QT study tested exposure at 5X the maximum recommended dose of 60 mg, it is possible that concomitant use of higher doses of ketoconazole would increase exposure to a range not studied in the thorough QT study.

In the opinion of the CDTL, the following deficiencies noted by the clinical pharmacology team are less likely to impact patient safety:

1. The quantitative aspects of the exposure-response-relationship including time course of the effect of tolvaptan and impact of a shorter than 24 hour dose interval has not been performed adequately. b(4)
2. A substantial fraction of the circulating total radioactivity (about 40%) has not been 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. Evidence for the identity of the postulated metabolites DM-4129-4133 was not provided.

6. Clinical Microbiology

Not relevant.

7. Clinical/Statistical - Efficacy

Proposed Indication:

Tolvaptan's proposed indication is for the treatment of hypervolemic and euvolemic hyponatremia and prevention of worsening hyponatremia.

The proposed dose is 15 mg tolvaptan PO daily, with dose titration to 30 mg at intervals of at least 24 hours, to a maximum dose of 60 mg daily as needed for effect.

Pre-submission Regulatory Activities:

Regulatory advice and agreements were well-summarized by Drs. Thompson and Targum:

The Division of Metabolism and Endocrinology Products had regulatory authority for the IND when it was originally submitted in 1997.

- End-of-Phase 2 Meeting: The Division emphasized the need to study subjects with serum sodium less than 130, to "...target the likely treatment population." The Division raised concern for off-label use in CHF patients and in this setting stressed need for cardiovascular safety and efficacy data before approval for use in hyponatremia. The sponsor was informed that exposure of only 30 days in the phase 3 studies was not likely not to be sufficient for safety. The Division also noted that 300 patients from the phase 3 studies of hyponatremia "might not be enough to address the cardiac adverse event question." (11/3/2002)
- Special Protocol Assessment Response: The Division advised the sponsor that the development program will need to show 1) that tolvaptan is effective in treating clinically significant (<130mEq/L) hyponatremia; 2) that for patients with mild hyponatremia, there is some clinical improvement associated with treatment beyond a change in a laboratory value; and 3) that tolvaptan is safe for all populations likely to receive the drug.
- Preliminary response for pre-NDA meeting scheduled with Division: "Given the limited number of hyponatremic subjects exposed to tolvaptan at six months and one year that fall significantly below ICH guidelines, it is unlikely that tolvaptan will be approved for indefinite treatment based on the current safety database. The approved duration of treatment will depend on the duration of adequate exposure in clinical trials and may be limited based on results of the safety review." (5/23/2006)
- IND transferred to Division of Cardiovascular and Renal Products. (4/6/2007)
- Pre-NDA meeting minutes: "Dr. Temple indicated the need for data for a significant number of patients with a serum sodium <130, where the usefulness of treatment is not in doubt." Concern was also raised by the Division of Metabolism and Endocrinology Products regarding tolvaptan's limited long-term safety database for hyponatremic patients. (5/7/2007)
- In the Division's response to proposed cognitive and neurologic outcome measures in protocol 156-04-246: If approval for a specific indication such as the treatment for cognitive and/or other neurological deficits accompanying hyponatremia was sought, further discussion with the Agency would be needed. "The existence of the entity (e.g., cognitive or other neurological deficits accompanying mild to moderate hyponatremia) and its operational definition must be broadly accepted by medical experts. Clinical trials should be appropriately designed to measure the effect of tolvaptan as a treatment for that entity, with suitable instruments being used for that purpose. (10/19/2007)

Efficacy

Two phase 3 studies, 156-02-235 and 156-03-238, provide the principal support of efficacy for the treatment of hyponatremia. The clinical development program was generally patterned after that of conivaptan, where the demonstration of efficacy was simply a demonstration that the drug increased serum sodium concentration.

Both phase 3 studies were randomized, double-blind, placebo-controlled trials in subjects with hyponatremia, defined as a serum sodium less than 135 mEq/L. Study 156-02-235 was conducted exclusively in the United States, study 156-03-238 was conducted inside and outside the United States. Subjects with non-hypovolemic hyponatremia were enrolled. Etiologies of hyponatremia included heart failure, cirrhosis, SIADH, and "other" etiologies. Subjects were stratified as having "mild" hyponatremia (serum sodium 130-134 mEq/L) or "severe" hyponatremia (serum sodium <130 mEq/L). Subjects received the test drug for 30 days, and were followed for 7 days after discontinuation (non-randomized withdrawal). Both protocols called for dose-titration; tolvaptan was initiated at a dose of 15 mg/day and could be titrated up to 60 mg as needed, based on serum sodium concentration.

Reviewer's Comment(s): It isn't clear to this reviewer how titration was handled in the placebo group, i.e., a greater fraction of subjects in the placebo group would have required upward-titration of the dose, which could have led to unblinding.

The co-primary endpoints for the phase 3 trials were the area under the curve (AUC) of the change from baseline serum sodium concentration through Day 4 and Day 30. An analysis of covariance (ANCOVA) model with factors of treatment, baseline hyponatremia severity and origin (2 x 3), and baseline serum sodium concentration as covariates were used for the analyses of the 2 primary efficacy endpoints. The baseline value was defined as the last measurement taken prior to the initial dose of study medication, and screening values were not used as baseline values. For missing data between 2 observations, the trapezoidal rule was used. For missing data following the last observation, the AUC was normalized to the mean daily AUC.

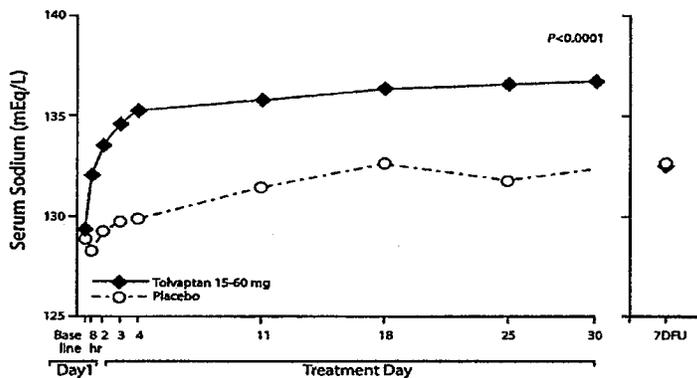
A total of 448 patients were randomized in the phase 3 studies; 223 subjects to placebo and 225 to tolvaptan. The median baseline serum sodium was close to 130 mEq/L; therefore, half of the subjects had a baseline that was <130 mEq/L. Due to concerns regarding data reliability at Sites 004 and 006 in 156-02-235 and Site 237 in 156-03-238, 24 subjects were excluded from the sponsor's efficacy analyses, as prespecified in the study's analytic plans.

Approximately 25% of subjects had an underlying diagnosis of SIADH, 33% had CHF, 27% had cirrhosis, and 21% had "other." Fifty-eight percent of subjects were female. Mean age was 61. In the US-only study (156-02-235), approximately 11% of subjects were of African ancestry (versus 1.6% in study 0156-03-238). Approximately 13% of subjects were fluid restricted at baseline.

For the primary efficacy endpoints in both studies, statistically persuasive increases in the average daily AUC of mean change from baseline in serum sodium concentration were observed in the tolvaptan groups versus placebo at Day 4 and Day 30. In a pooled analysis, this represented an average daily mean change of 4.0 mEq/L for tolvaptan and 0.4 mEq/L for placebo; the changes through Day 30 were 6.2 mEq/L and 1.8 mEq/L for tolvaptan and placebo, respectively. The 1^o medical officer noted that discontinuation rates were high. Whereas more than 90% of subjects had Day 4 measurements, approximately 24 and 29% of tolvaptan and placebo-treated subjects, respectively, did not complete the trial. However, given the magnitude of the treatment effect, the missing data would not likely affect the overall Day 30 results. Moreover, more patients discontinued treatment in the placebo arm, particularly in the subgroup with more severe hyponatremia, suggesting that lack of efficacy (of placebo) was operational, and not tolvaptan-related side effects.

Subgroup analyses: The results were consistent across subgroups of hyponatremia etiology, volume status (normovolemic; hypervolemic), sex, age, and race (although most subjects were Caucasian). Importantly, results were consistent in subgroups of subjects categorized by baseline serum sodium concentration.

The sponsor's proposed figures for labeling, titled: "SALT-1 STUDY: Analysis of Change from Baseline in Serum Sodium (mEq/L) by Visit" should be revised to show standard deviations, and should have a double hash mark inserted in the lower y-axis to emphasize that the serum sodium concentrations do not begin at zero. (This practice exaggerates the apparent effect size.)



Prevention of worsening hyponatremia: The sponsor's proposed labeling includes the prevention of worsening hyponatremia as an indication for tolvaptan. Prevention of worsening was shown fairly convincingly in a number of post-hoc analyses, but none appears to have been to have been pre-specified, in fact, none are shown in the study reports for the phase 3 trials. A more fundamental question is whether the claim is self-evident, and therefore unwarranted. For example, erythropoietins are indicated for the treatment of anemia in various clinical settings. No doubt, they prevent worsening anemia, but such a claim would be frivolous. The conivaptan package insert lacks this claim, and this reviewer sees no reason to provide the claim for tolvaptan.

Data on hyponatremia from studies of CHF: Six CHF trials included subjects with hyponatremia; however, changes in serum sodium concentration were not the primary study objectives. Serum sodium concentrations were assessed at multiple time points without any prespecified analytic plan. Thus, these findings should be viewed only as providing supportive evidence of tolvaptan's efficacy. In general, the studies enrolling substantial numbers of subjects with hyponatremia (studies 156-03-237, 156-98-213, and 156-97-252) demonstrated greater improvements in serum sodium concentration in tolvaptan-treated subjects than placebo-treated subjects, and greater proportions of subjects with normalization of serum sodium in the tolvaptan arms. Viewed as a whole, the Combined Clinical and Statistical Review team opined that these studies support tolvaptan's efficacy in increasing serum sodium concentration.

The key issues regarding the sponsor's demonstration of efficacy are discussed below:

1. What kinds of subjects were included in the studies?

Entrance criteria were essentially the same in studies 156-02-235 and 156-03-238:

Inclusion criteria included:

- subjects with euvolemic and hypovolemic hyponatremia defined as serum sodium concentration < 135 mEq/L

Exclusion criteria included subjects with:

- hyponatremia who would likely require IV saline for correction of symptomatic or asymptomatic severe hyponatremia during the course of the study
- acute and transient hyponatremia associated with head trauma or postoperative states

- serum sodium <120 mEq/L with associated neurologic symptoms (e.g., apathy, confusion, seizures)
- receipt of other agents for hyponatremia within 7 days of randomization (IV saline may have been used prior to the screening period in study 156-03-238, only)
- serum creatinine >3.5 mg/dL.

It should be apparent, therefore, that subjects who truly *required* treatment for hyponatremia (IV saline) were not enrolled by intention. Chronicity of hyponatremia was not a criterion for study entry; subjects with acute, subacute, or chronic hyponatremia were enrolled, although subjects with acute hyponatremia associated with head trauma or post-operative states were excluded. There was no lower limit for serum sodium concentration at study entry, except that subjects with serum sodium concentrations <120 mEq/L were excluded if there was evidence of neurological impairment.

These criteria tended to select subjects with mild or moderate hyponatremia, who were not symptomatic, or at least not sufficiently symptomatic to require IV saline. Subjects with more severe hyponatremia (sodium <120 mEq/L) could be enrolled, but had to be relatively symptom-free in order to gain study entry.

2. What was the clinical benefit?

Following review of a Special Protocol Assessment, the Division of Metabolism and Endocrinology Products advised the sponsor that the study would need to show that: 1) tolvaptan treatment is effective in treating clinically significant hyponatremia (sodium <130 mEq/L); and 2) that there is some tangible clinical improvement beyond a change in a laboratory value for subjects with mild hyponatremia (sodium \geq 130 mEq/L).

The sponsor succeeded in demonstrating effectiveness in increasing serum sodium concentrations, even in subjects with baseline sodium concentration <130 mEq/L. Such subjects comprised about half of all subjects in the phase 3 hyponatremia studies, and tolvaptan was efficacious in this subset.

The establishment of clinical benefit in subjects with baseline serum sodium concentrations >130 mEq/L was addressed by a 2° endpoint. The analytic plans of the two phase 3 hyponatremia studies each specified 15 identical 2° efficacy endpoints: 9 were focused on some aspect of serum sodium concentration, 3 were based on changes in fluid balance or weight, and 2 were based on need for alternative therapies (fluid restriction or saline infusion). A single 2° endpoint, a patient-reported outcome (PRO) based on the SF-12 health survey, had the potential to demonstrate a tangible clinical benefit to subjects in the trials. The protocols did not include a pre-specified priority sequence or plan for alpha spending for the 2° endpoints; in essence, some of the 2° endpoints were sensitivity analyses on the 1° endpoint, and others should be considered exploratory.

In both studies, the 9 secondary endpoints based on serum sodium concentration demonstrated statistically significant improvements for tolvaptan over placebo. The 2° endpoints that were focused on fluid balance and weight reached statistical significance in favor of tolvaptan, except that the difference in body weight at Day 1 was not statistically significant in study 156-03-238. Neither of the 2° endpoints based on the need for alternative therapies (fluid restriction or saline infusion) reached statistical significance in either study.

Changes from baseline in the SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) were calculated using the methods developed by J. Ware, et. al. For both studies, changes from baseline in both scales were analyzed using an ANCOVA model at Week 1 (or Week 2¹) and Day 30, respectively. Both observed cases (OC) and last observation carried forward (LOCF) analyses were applied to the analyses at Day 30. Therefore, within ¹each of the two studies, 2 endpoints (PCS and MCS) were evaluated at 2 time points (Week 1 [or Week 2] and Day 30), and 2 statistical methodologies (OC and LOCF) were used at the Day 30 time points. Thus, even if the PRO endpoint is considered in isolation (i.e., if the multiplicity issue inherent in considering the other 14 secondary endpoints is ignored), for each study, there were 6 ways to achieve a statistical “win” on the PRO instrument: 2 scores (PCS or MCS), at two times (Week 1 or 2 or Day 30), with two methods for handling missing data at Day 30 (OC or LOCF).

There was a statistically significant improvement in the MCS in study 156-02-235; however, improvement was demonstrable in only one of two scales (MCS, and not PCS), and only at Day 30 (Day 30 results were statistically significant irrespective of the method used for handling missing data). For study 156-03-238, the results were not statistically significant on MCS or PCS.

There were several additional issues that further compromised the interpretability and/or persuasiveness of the PRO results:

Overall, 37% of the overall data were missing, and there is no way to know whether data were missing at random, which undermines the interpretation of the finding.

The Study Endpoints and Label Development (SEALD) Team raised serious concerns regarding the PRO instrument. They noted that the items included in the SF-12 do not address symptoms typical of hyponatremia, and that content validity of SF-12 has not been established in a clinical study setting. In addition, they noted that the MCS and PCS included items that are not direct measures of mental and physical functioning, respectively.

PRO instruments are, by definition, subjective, and it is likely that substantial unblinding occurred that would have served to bias the results of the studies. Potential sources of unblinding include: 1) unblinding of subjects and caregivers, given that tolvaptan treatment was associated with greater thirst and urine output (approximately 1.2 liter/day in the two studies), 2) unblinding of healthcare professionals who had access to serum sodium results (these may have led to some unblinding of subjects as well, if the lab results were communicated to the subject), and 3) unblinding of subjects and caregivers, given that virtually all subjects in the placebo group would have required up-titration of their placebo “dose.”

In light of these important issues - - positive results for only one of two endpoints at one of two time-points in one of two trials, lack of content validity, missing data, and potential unblinding, the PRO endpoint is unpersuasive, fails to meet regulatory standards for demonstration of efficacy, and is unusable for labeling in my opinion.

¹ Week 1 was used as in one of the studies; Week 2 in the other.

8. Safety

Adequacy of the safety database:

_____ and because CHF is one of the causes of hyponatremia, there is some overlap between the patient populations in the multiple-dose studies. Thus, within the hyponatremia studies, a subset of subjects had CHF as the underlying disease. Conversely, in the studies of CHF, a minority of subjects had hyponatremia. For the purpose of the assessment of safety, all subjects with hyponatremia are included in the analysis, irrespective of whether they were enrolled in studies of hyponatremia or studies of CHF. Subjects with CHF who were normonatremic are considered as separately as a supportive data set. b(4)

In total, 3294 subjects with CHF and/or hyponatremia received tolvaptan in multiple-dose, placebo-controlled trials. Of these subjects, only 607 subjects had hyponatremia, defined as a serum sodium <135 mEq/L. Thus, the vast majority of the safety experience was obtained in subjects with CHF, but without hyponatremia. Moreover, these subjects were largely enrolled in a single trial (156-03-236) and received 30 mg of tolvaptan _____. b(4)

With respect to the 607 subjects with hyponatremia, there are a number of important limitations:

1. Severity of hyponatremia: Approximately two-thirds of the 607 subjects (418) had mild hyponatremia, with baseline serum sodium concentration 130 to 134 mEq/L. Only one-third of these subjects (189) had more significant hyponatremia, with baseline serum sodium concentration <130 mEq/L. Within the <130 mEq/L subset, 52 subjects had a baseline <125 mEq/L and 8 had a baseline <120 mEq/L.
2. Underlying disease: Two-thirds of these 607 subjects had CHF; only 97 subjects carried a diagnosis of SIADH/other, and 100 subjects had hyponatremia in the setting of cirrhosis.
3. Dose: The exposure to tolvaptan is somewhat limited at the high end of the dosage range. Specifically, in placebo-controlled trials, 192 subjects were exposed to a tolvaptan dose of 60 mg daily, with a few dozen more exposed to 60 mg in an uncontrolled, open-label extension study.
4. Treatment duration: With 607 hyponatremia subjects exposed to any duration of tolvaptan treatment, just half (311 subjects) were exposed for ≥ 1 month, 132 were exposed for ≥ 6 months, and only 69 were exposed for ≥ 1 year. Of these 69 subjects, 56 had a baseline sodium of 130 to 134 mEq/L, and 13 had a baseline serum sodium <130 mEq/L. Also of note, all of the subjects followed for longer periods of time had hyponatremia in the setting of heart failure. Beyond 30 days, there are no placebo-controlled data from subjects with hyponatremia due to SIADH/other or cirrhosis. With respect to all of the subjects exposed to tolvaptan (including those without hyponatremia), 817 subjects received tolvaptan for at least a year (the vast majority of these subjects had heart failure without hyponatremia, and received 30 mg tolvaptan).

The "supportive" data set is substantially larger, and includes subjects with CHF who were not hyponatremic. These data include 3147 subjects of the total population of 3294 subjects who

received tolvaptan. The CHF patient population is quite “fragile;” CHF patients are at considerable risk of adverse events, particularly cardiovascular events, and a substantial fraction of these are serious and life threatening. With respect to reassurance about safety, these data can be regarded in three ways:

- The first is to consider that the CHF population is “enriched” with significant risk factors that predispose to adverse events. If a drug appears to be relatively “safe” in this population, then this reassurance may be extrapolated to a less ill patient population, for surely the latter group is less at risk and less likely to experience adverse effects. For example, one might expect to detect negative inotropic effects, hypotension, or renal insufficiency in a CHF patient population, given the sensitivity of this population to such effects.
- Conversely, a high-risk CHF patient population has the potential to mask safety issues that might be detectable in a healthier patient population, and would be important to detect and recognize. For example, a drug with proarrhythmic effects might be associated with an increased risk of sudden death, from 0.1% (placebo) to 3.1% (drug) in a patient population that is not at particular risk of sudden death. This small but clinically important absolute risk would go virtually undetected in a CHF patient population, where sudden death is not unusual.
- The sheer size of the CHF data set provides a measure of comfort regarding less common adverse events that would be expected to be detectable against the background of adverse events commonly encountered in a CHF population, e.g., agranulocytosis.

Here the data are complementary, and can be considered in all of these lights.

Deaths:

Over the entire development program, deaths were fairly evenly divided between tolvaptan and placebo groups, with mortality of 651/3536 (18.4%) and 620/2800 (22.1%) in the two treatment groups, respectively. Examination of various subgroups yielded some imbalances in mortality, but of course this is a “zero sum game.” The clinical review team examined mortality as a function of dose, but few subjects were exposed to doses outside of the 15 to 60 mg dose range, making the results difficult to interpret. Moreover, with use of a titrated therapy, subjects with a greater burden of disease are expected to be more resistant to treatment. Under these circumstances, it is not surprising that higher doses are associated with worse outcomes.

Serious Adverse Events:

The clinical review team pointed out slightly higher incidences of cardiac arrest (1.5 vs. 0.9%), ventricular tachycardia (2.2 vs. 1.8%), cardiogenic shock (1.1 vs. 0.9%), and syncope (1.2 vs. 1.0%) in tolvaptan-treated subjects versus controls, respectively, but noted that the absolute differences between tolvaptan and placebo subjects were small. Using the pooled terms ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia and ventricular tachycardia, the frequency was 8.1% in the tolvaptan group and 7.1% in placebo controls. When the terms “cardiac arrest” and “cardiorespiratory arrest” were pooled, the difference between groups was minimal.

This reviewer re-coded all of the adverse events in the tolvaptan development program, including those reported in the 120-Day Safety Update. Results for serious adverse events are shown in the table, below.

Cardiac Rhythm:

For the pooled terms “cardiac arrest,” “sudden cardiac death,” “asystole,” and “electromechanical dissociation,” there were 3 events in tolvaptan-treated subjects in SALT I and II (1.3%), versus none in the placebo group. In the larger CHF study, the percentages were similar (7.6 and 7.0% in tolvaptan and placebo subjects, respectively). In the hyponatremia subset of the large CHF study, the frequencies of ventricular fibrillation were 2.9 and 0.9% in the tolvaptan and placebo groups, respectively. However, because the numbers of serious rhythm disturbances are small, and given that mortality is similar in the two treatment groups, there doesn't appear to be an important signal here. My conclusion is identical to that of the primary reviewer.

Differences in serious adverse events are most notable for bleeding (worse for tolvaptan: 3.6 vs. 0.9% in SALT I and II; 2.9 vs. 2.6% in the large CHF study), and dehydration/volume depletion (1.8 vs. 0.5%).

Bleeding: With respect to bleeding, the clinical reviewer pointed out that this was mostly attributable to bleeding in subjects with cirrhosis:

“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.”

She suggested that the safety database in cirrhotic patients is insufficient to establish tolvaptan's safety. Moreover, she opined that in light of the bleeding, it would be desirable to demonstrate a tangible clinical benefit in this population, aside from simply increasing serum sodium, prior to approval. The Advisory Committee was also concerned about bleeding in subjects with cirrhosis (see 9). This reviewer agrees with these assessments, and the concern seems sufficient to support a contraindication or warning for use in patients with cirrhosis. Of note, pre-clinical studies suggested that tolvaptan could affect vitamin-K-dependent clotting factors and platelet function.

Dropouts and Discontinuations:

Dropouts and discontinuations provide little insight into the tolerability and safety of tolvaptan in this development program. In multiple-dose, placebo controlled trials, the incidences of discontinuations were similar in tolvaptan and placebo-treated subjects (approximately 35% in each). Discontinuations due to adverse events were more common in tolvaptan-treated subjects (9.5%) than placebo-treated subjects (7.2%), whereas discontinuations due to withdrawal of consent were more common in the placebo subjects (9.4%) than tolvaptan-treated subjects (8.2%).

In the large phase 3 heart failure trial, 6.5% of tolvaptan-treated subjects and 5.5% of placebo-treated subjects discontinued treatment due to an adverse event. Of the adverse events leading to discontinuation, only thirst, dry mouth, hyperkalemia, and cardiac failure were

reported in tolvaptan-treated subjects at an incidence more than 0.2% greater than that observed in the placebo group. Three tolvaptan-treated subjects (0.3%) discontinued treatment due to hypernatremia. In the phase 3 hyponatremia trials, 10.3% and 11.8% of tolvaptan and placebo-treated subjects, respectively, discontinued trial medication due to an adverse event. No single adverse event leading to discontinuation occurred at an incidence >1% in the tolvaptan treatment arm.

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Serious Adverse Events	SALT I & II All Hyponatremia		Large CHF Study 236		Large CHF Study 236 Hyponatremia Subset	
	tolvaptan n=223	placebo n=220	tolvaptan n=2063	placebo n=2055	tolvaptan n=242	placebo n=232
	CHF or pulm edema	14 (6.3)	9 (4.1)	766 (37.1)	730 (35.5)	123 (50.8)
CHF	14 (6.3)	9 (4.1)	752 (36.5)	716 (34.8)	121 (50)	117 (50.4)
infection	12 (5.4)	10 (4.5)	208 (10.1)	236 (11.5)	24 (9.9)	37 (15.9)
cardiac arrest: sudden cardiac death: asystole, electromechanical dissociation	3 (1.3)	0 (0)	156 (7.6)	148 (7)	27 (11.2)	22 (9.5)
arrhythmia	3 (1.3)	3 (1.4)	149 (7.2)	128 (6.2)	19 (7.9)	16 (6.9)
pneumonia	3 (1.3)	3 (1.4)	94 (4.6)	92 (4.5)	17 (7)	15 (6.5)
ventricular arrhythmia	1 (0.4)	2 (0.9)	81 (3.9)	65 (3.2)	13 (5.4)	8 (3.4)
tachycardia	1 (0.4)	2 (0.9)	71 (3.4)	65 (3.2)	7 (2.9)	9 (3.9)
cerebrovascular accident, transient ischemic attack	1 (0.4)	1 (0.5)	68 (3.3)	52 (2.5)	7 (2.9)	3 (1.3)
bleeding	6 (3.6)	2 (0.9)	59 (2.9)	53 (2.6)	8 (3.3)	0 (4.3)
cerebrovascular accident	0 (0)	1 (0.5)	57 (2.8)	46 (2.2)	6 (2.5)	3 (1.3)
supraventricular arrhythmia	2 (0.9)	0 (0)	51 (2.5)	49 (2.4)	4 (1.7)	5 (2.2)
non-sustained ventricular tachycardia (VT), or VT unspecified	0 (0)	2 (0.9)	47 (2.3)	37 (1.8)	3 (1.2)	6 (2.6)
angina	0 (0)	0 (0)	44 (2.1)	50 (2.4)	2 (0.8)	6 (2.6)
acute myocardial infarction	1 (0.4)	0 (0)	41 (2)	53 (2.6)	4 (1.7)	6 (2.6)
sepsis	3 (1.3)	4 (1.8)	40 (1.9)	33 (1.6)	8 (3.3)	6 (2.6)
unstable angina, acute coronary syndrome	0 (0)	0 (0)	39 (1.9)	38 (1.8)	2 (0.8)	6 (2.6)
pre-syncope or syncope	1 (0.4)	0 (0)	39 (1.9)	25 (1.2)	5 (2.1)	5 (2.2)
cardiogenic shock	1 (0.4)	0 (0)	37 (1.8)	24 (1.2)	9 (3.7)	7 (3)
dehydration, volume depletion	4 (1.8)	1 (0.5)	37 (1.8)	26 (1.3)	7 (2.9)	2 (0.9)
chest pain (not angina, or unknown source)	3 (1.3)	3 (1.4)	36 (1.7)	34 (1.7)	1 (0.4)	5 (2.2)
syncope	1 (0.4)	0 (0)	35 (1.7)	24 (1.2)	4 (1.7)	5 (2.2)
hypotension	2 (0.9)	4 (1.8)	34 (1.6)	26 (1.3)	5 (2.1)	8 (3.4)
apnea, respiratory failure, cyanosis, hypoxemia, desaturation	4 (1.8)	2 (0.9)	34 (1.6)	38 (1.8)	6 (2.5)	4 (1.7)
dyspepsia, nausea, vomiting, indigestion, epigastric pain, gastritis, duodenitis, gastric ulcer, <i>H. pylori</i> infection	3 (1.3)	2 (0.9)	34 (1.6)	35 (1.7)	4 (1.7)	5 (2.2)
coronary artery disease myocardial ischemia	0 (0)	1 (0.5)	33 (1.6)	43 (2.1)	1 (0.4)	5 (2.2)
atrial fibrillation	1 (0.4)	0 (0)	33 (1.6)	34 (1.7)	2 (0.8)	3 (1.3)
pulmonary edema	0 (0)	0 (0)	28 (1.4)	29 (1.4)	4 (1.7)	2 (0.9)
gastrointestinal hemorrhage	5 (2.2)	1 (0.5)	28 (1.4)	29 (1.4)	3 (1.2)	6 (2.6)
anemia	1 (0.4)	2 (0.9)	27 (1.3)	29 (1.4)	1 (0.4)	4 (1.7)
ventricular fibrillation	0 (0)	0 (0)	26 (1.3)	23 (1.1)	7 (2.9)	2 (0.9)

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Other Adverse Events:

The clinical review team focused on pulmonary embolism, stroke, atrial fibrillation, and coma, and found no compelling associations between tolvaptan and these events.

Overly Rapid Correction of Serum Sodium:

The goal of treating hyponatremia is to increase serum sodium levels; however, overly rapid correction is associated with 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. Because of this concern, coma and similar central nervous system events were carefully considered by the clinical review team. There were no clear cases of osmotic demyelination observed in the tolvaptan development program.

To minimize this risk, current guidelines recommend rates of correction of < 10-12 mEq/L over 24 hours. In the phase 3 hyponatremia trials, serum sodium was assessed at 8 hours post-dose on Study Day 1 and daily until discharge. At the 8-hour measurement, 11 tolvaptan-treated subjects (5.3%) experienced an increase in sodium >8 mEq/L; at 21 hours, 2 (1.1%) had an increase >12 mEq/L. In contrast, <1% of placebo-treated subjects experienced an increase >8 mEq/L at 8 hours, and none experienced an increase >12 mEq/L. Overly rapid rates of correction were more common in subjects with underlying SIADH/Other and those with a baseline serum sodium < 130 mEq/L. In all of these subjects, overly rapid correct occurred despite free access to water.

Of the subjects with an overly rapid rise in sodium, 4 experienced adverse events coincident with the period of rise. One subject (PID 02235-035-2002) developed hypotension, dehydration, ataxia, and slurred speech concomitant with the rise (9 mEq/L increase by approximately 9.5 hours after tolvaptan initiation). Adverse events of thirst, lightheadedness, hypokalemia, increase in hypertension and changes in urination (increase and "strong urge") were also reported. One subject withdrew consent. In searching the database, the clinical review team identified an additional subject with "sodium rise 13 point in 24 hours." The subject (PID 03238-137-3021) developed a rapid rise in serum sodium, hypernatremia, and acute renal failure, and ultimately died. A brief narrative is provided:

Subject 03238-137-3021 was 80 year-old man with a history of NYHA Class IV heart failure and baseline serum sodium 131 mEq/L whose serum sodium increased from 128mEq/L on Day 2 to 142 mEq/L on Day 3 (+13 mEq/L). The study medication was withdrawn following the Day 2 dose. Sodium rose to 153-160 mEq/L on Day 5 and then reportedly fell to 130 mEq/L on Day 6. The subject developed acute renal failure (creatinine rise from 1.7 to 2.1; blood urea nitrogen rise from 53 to 83) concurrent with the event. The subject died on Day 6.

The Clinical Reviewer commented that "Tolvaptan's role in this death and the precipitation of acute renal failure (suspected prerenal) cannot be excluded."

This reviewer would note, in addition, that the subject's tolvaptan dose appears to have been managed correctly. In other words, the Day 1 dose was appropriately administered, based on a serum sodium of 131 mEq/L. The Day 2 dose was appropriately administered, as well, after which the sodium increased to 142 mEq/L, and no additional drug was administered.

The case serves to illustrate that serum sodium can rise suddenly and unexpectedly, despite reasonable labeling instructions.

A warning on overly rapid sodium correction would be appropriate for labeling. Moreover, hospitalization may be necessary when initiating therapy, to achieve the level of monitoring needed to guide initial treatment and dose titration.

9. Advisory Committee Meeting

The Cardiovascular and Renal Drugs Advisory Committee met on June 25, 2008 to discuss the hyponatremia indication for this NDA.

Question 1: The Committee was presented with a list of symptoms and signs (death, coma, seizure, altered consciousness, mental dulling/slowing, attention deficit, confusion, disorientation, agitation, obtundation, lethargy, lassitude, muscle tremor/cramping, ataxia, gait disturbance, focal neurological signs, falls, forgetfulness, fatigue, dizziness, headache, nausea, vomiting, thirst, loss of appetite, taste disturbance, social withdrawal, and malaise), and asked whether any are attributable to hyponatremia, rather than the underlying disease. The Committee opined that all have the potential to be attributed to hyponatremia, but that they are non-specific, and that their manifestation is related in part to the rapidity with which hyponatremia develops.

Question 2: The Committee agreed that the sponsor's development program demonstrated effects on serum sodium levels across the different underlying diseases (SIADH, cirrhosis, heart failure) and over the range of observed baseline sodium levels (including lower baseline values). They also agreed that the results were sustained during long-term use (at least 30 days).

Question 3a: The Committee was asked to opine on the SF-12 patient-reported outcome instrument, with particular regard to its content validity, ability to demonstrate clinical benefit in the hyponatremia setting, magnitude of change commensurate with clinical benefit, and overall conclusion. In general, the committee was untroubled by the lack of content validity, and agreed that the instrument was detecting something of clinical relevance. The committee also discussed the marginal statistical persuasiveness of the findings (one test out of two in one study out of two).

Question 3b: The Committee was asked to comment on the utility of the Hyponatremia Disease-specific Survey (HDS) and the Kansas City Cardiomyopathy Questionnaire. The Committee found little evidence for clinical benefit in the results from these instruments.

Question 4: The Committee was asked to comment on other benefits of treating hyponatremia that might have been shown in the sponsor's development program, e.g., salutary effects on neurological or cognitive function. Most committee members agreed that the sponsor did not show convincing evidence of improvement in neurological or cognitive function.

Question 5: On the question of whether there is adequate evidence that tolvaptan can be expected to produce clinical benefits in the treatment of patients with chronic hypervolemic or euvolemic hyponatremia, the results were 8 in favor and 3 against. The consensus was that a low serum sodium is not medically desirable, and that many patients need to be treated. There seemed to be some agreement that a serum sodium concentration below 130 mEq/L would be

11. Other Relevant Regulatory Issues

None of the inspections uncovered issues that impact importantly on the integrity of the data or the approvability of the application.

12. Recommendations/Risk Benefit Assessment

Recommended regulatory action:

I recommend approval of tolvaptan for the treatment of euvolemic and hypervolemia for patients with a serum sodium below 130 mEq/dL (if symptomatic), or below 125 mEq/L (whether symptomatic or not). These thresholds are in line with the discussion at the Cardiovascular and Renal Drugs Advisory Committee Meeting of June 25, 2008. There should be a warning or contraindication for patients with cirrhosis. If the REMS (see below) can not be worked out with the sponsor, a *complete response* is appropriate for now, with outright approval once REMS are agreed upon. A Medguide should be developed to educate patients regarding risk mitigation.

Detailed Rationale:

The NDA provides abundant evidence that tolvaptan causes aquaresis, leading to increases in serum sodium concentration. Though the safety database is limited with respect to number of subjects and duration of exposure, particularly for the intended patient population, there is no evidence to suggest that the drug acts in an unpredictable way, i.e., there appears to be mechanistic plausibility for all of the known effects of the drug. The key safety concerns are overly rapid rise in serum sodium concentration, and use in appropriate patient populations. Specifically, intensive monitoring of electrolytes is important when therapy is initiated (meaning that treatment should be initiated in an inpatient setting), and particular groups of patients should not be treated. These groups include:

- Patients in whom urgent correction of serum sodium is needed (when there are neurological signs or symptoms, or when they seem impending). Such patients were not studied in the development program, and tolvaptan's performance characteristics and safety are unproven here.
- Patients who lack access to free water
- Patients who are unable to sense thirst
- Patients with hypovolemic hyponatremia
- Patients with cirrhosis (a "fragile" population where safety data are limited, and there appears to be excess bleeding, consistent with pre-clinical data suggesting that the drug could both deplete vitamin-K-dependant clotting factors and inhibit platelet aggregation)

appropriate for treatment; however, the patient's symptoms, duration of hyponatremia, and underlying disease state should be considered. A couple of members stated that they would treat patients with heart failure who were hyponatremic.

Question 6a: The Committee was asked whether there safety issues that impact approvability/findings of concern. Various members of the Committee noted that bleeding was a concern, particularly in patients with cirrhosis. Some members suggested that patients should be hospitalized when treatment is initiated. Another expressed concern regarding patients who have a condition or situation where they are not able to "follow their thirst." There was also concern about use of the drug in pregnancy, given that pregnancy is a common cause of hyponatremia.

Question 6b: The Committee was asked whether there are sufficient data upon which to base a decision. The lack of long term safety data was noted as a concern. Committee members also wanted more data on the people who were excluded from the study and other specific populations.

Question 7: On the question of whether tolvaptan should be approved for use in the chronic treatment of hypervolemic or euvolemic hyponatremia, the vote was 8 in favor of approval and 3 against. Discussion followed concerning where (inpatient/outpatient) treatment should be initiated and the duration of chronic therapy. The members made several comments regarding the generalizability of safety and clinical benefit data from the development program to the larger population of patients who would be treated, particularly patients with sodium levels below 130 who may be most likely to be treated.

In terms of a threshold for treating patients with hyponatremia, the most direct opinion was voiced by the sponsor's expert, Dr. Joseph Verbalis. He opined (this quote cited from a preliminary transcript of the meeting):

"So, anyone with a serum sodium under 125, in my opinion, should be treated because of the possibility of moving into that state. Anyone with a serum sodium between 125 and 130 should be treated if they have demonstrable symptoms. And, anyone without symptoms, including the vast majority of the people between 130 and 134 should not be treatment candidates unless they meet one of the specific criteria, such as recurrent hospitalization for hyponatremia or, as described in the psychiatric patient population, recurrent seizures that clearly improve with treatment of their hyponatremia."

10. Pediatrics

The Pediatric Review Committee discussed the NDA and a proposed pediatric study on August 13, 2008. The Committee expressed concern that the sponsor's pediatric proposal in subjects

The Committee opined that a waiver in children aged 0-5 seems acceptable based on the proposed labeling.

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- Patients who are pregnant or breastfeeding
- Children (there are no data)

The main problem for approval is the discomfort in unleashing a product based solely on a change in a laboratory parameter. For some diseases, the main laboratory parameter doesn't begin to represent the overall scope of the disease (e.g., glucose in diabetes), whereas in other disease states, the parameter defines the disease as well as its severity (e.g., hypokalemia, anemia). Hyponatremia seems to fit better with the latter group than the former. Nevertheless, there are good reasons to be suspicious regarding surrogates. With little question, the Agency has accepted lowering of LDL cholesterol (statins and others) and increasing hematocrit (recombinant erythropoietin and others) as tantamount to efficacy, but recently even these drugs have come under scrutiny. For this application, the key question relates to quantifying benefit and risk when there is no tangible symptom relief for an individual patient. How many patients need to experience a 5 mEq/L increase in serum sodium concentration in order to offset one variceal bleed? This is a difficult calculus.

Thus, approval of tolvaptan for hyponatremia requires acceptance of an increase in serum sodium concentration as a benefit *in and of itself*: that simply correcting the abnormality is a benefit, independent of any improvement in symptoms. The development program was geared to show an increase in serum sodium, and it is not surprising that the application provides little evidence that tolvaptan improves clinical benefit in a meaningful and tangible way. In retrospect, there was no way for the development program to show symptom relief, given that symptomatic subjects were largely excluded from participation in the studies. All of this notwithstanding, the Advisory Committee was generally willing to accept serum sodium as an acceptable surrogate endpoint, and it seems appropriate to accept their recommendation.

The indication statement should be written with a specific threshold(s) for treatment. The threshold serum sodium concentration for treating patients with symptoms would be higher than the threshold for treating patients without symptoms. This is somewhat peculiar, in that tolvaptan has not been shown to improve symptoms. Nevertheless, it seems reasonable to assume that symptoms will improve as the sodium concentration rises. Asymptomatic patients with mild hyponatremia should not receive treatment, and for such patients, the threshold serum sodium concentration should be lower. Based on the deliberations of the Advisory Committee, and in particular the opinions of Dr. Joseph Verbalis, patients with a serum sodium concentrations <125 mEq/L would be candidates for treatment with tolvaptan irrespective of symptom status. Between 125 and 130, patients could be treated if symptomatic. Prescribers need also be advised that the drug has not been shown to improve symptoms in patients with hyponatremia.

The safety database is only marginally adequate; it has probably detected the common and expected adverse events, but provides little confidence regarding less common events. Again, the heart failure database is quite sizeable, and provides reassurance for adverse events that are not common or typical in the CHF patient population. Unfortunately, many of the events for which we would like to gain reassurance are common in the CHF population, so these data are only marginally helpful.

Recommendation for Postmarketing Risk Management Activities:

1. A good argument can be made to provide a warning or contraindication for patients with cirrhosis (and the primary Medical Officer made this argument). For this indication, the data suggest that the risk-benefit is suboptimal; however, the experience is really too limited to draw

any firm conclusions at this point. It is possible that a larger study would provide more confidence about safety. If the labeling carries a warning for cirrhosis, a study to gain more experience in cirrhosis patients would be a reasonable post-marketing requirement. If the labeling carries a contraindication, then it would be in the sponsor's own interest to initiate such a study, and a post-marketing requirement seems unnecessary.

2. A pediatric study will be needed, and the details will need to be worked out. The inclusion/exclusion criteria will need to be congruent with the indicated adult patient population.

3. The company will need to develop a risk management strategy to ensure that patients are appropriately monitored when treatment is initiated. Presumably, this means that initiation would be restricted to the inpatient setting, and mechanisms would be in place to assure this.

4. Because patients themselves can mitigate the risks of tolvaptan treatment, the sponsor should develop a Medguide. Specifically, patients should be advised that: 1) they should not be initiating treatment at home (they should have been started in a hospital); 2) they should not use tolvaptan if they don't have free access to water; 3) they should not use tolvaptan if they are incapable of sensing thirst; and 4) if they discontinue tolvaptan on their own, they should not restart treatment.

5. Per the CMC Team, within 2 months of approval, "Otsuka agrees to submit the validation report of [REDACTED] and consequent replacement of the dissolution test for the [REDACTED] [REDACTED] as a supplement. Full validation data for the [REDACTED] method will also be included in the supplement."

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/s/

Ellis Unger
8/21/2008 01:42:04 PM
MEDICAL OFFICER