

NDA 22-275: Tolvaptan for the Treatment of Hypervolemic and Euvolemic Hyponatremia and for Prevention of Worsening Hyponatremia

FDA Review of Patient-Reported Outcome (PRO) Measures for the Hyponatremia Indication

EXECUTIVE SUMMARY:

This review focuses on the key patient-reported outcome (PRO) endpoints that were utilized in the tolvaptan clinical trials to support the indication of tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia and for prevention of worsening hyponatremia (Studies 156-02-235 and 156-03-238). Only the treatment of hyponatremia is being considered in this review and therefore, the PRO endpoints used in the tolvaptan clinical trial (Study 156-03-236) to evaluate tolvaptan for the short-term treatment of the signs and symptoms of worsening heart failure beyond that achieved with standard of care are not discussed here. These instruments, which include the Patient-Assessed Global Clinical Status, Dyspnea Status Instrument and the Kansas City Cardiomyopathy Questionnaire, are not measures of the signs and symptoms of hyponatremia, and therefore, are not included in this summary. In addition, the Hyponatremia Disease-Specific Survey, which was used as an exploratory endpoint in Study 156-03-238, is not discussed in this summary. Supportive information to justify that this instrument represents an adequate and valid measurement of the signs and symptoms of hyponatremia has not been submitted for FDA review.

The principle PRO instrument used in the tolvaptan clinical trials for the hyponatremia indication to support efficacy was the 12-Item Short Form Health Survey (SF-12). The FDA review of the development and utilization of this instrument includes only information that was submitted by the sponsor as of May 21, 2008. Because the NDA submission omitted important information (e.g., scoring algorithms), the review is not comprehensive.

Based upon the submitted information, the FDA has concluded that the SF-12 does not adequately define a clinically significant treatment effect for the target population of patients and therefore, cannot support efficacy claims. The SF-12 was developed as a measure of overall health status and does not measure the signs and symptoms of hyponatremia, including the neuro-cognitive manifestations of hyponatremia. There is an absence of content validity, defined as evidence that the instrument represents a meaningful, complete, interpretable, and appropriate measurement of treatment benefit (how a patient survives, feels, or functions), in the target patient population. Therefore, since the SF-12 cannot effectively define the treatment benefit in patients with hyponatremia, it cannot support efficacy claims related to treatment in this target population.

This review summarizes FDA's position by first defining several basic principles used to formulate conclusions, which are derived from the draft Guidance, "*FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.*"¹ Subsequently, a brief description of the key PRO instrument, the SF-12, used

in the tolvaptan clinical trials as a secondary endpoint to support efficacy claims will be presented.

FDA PRO REVIEW PRINCIPLES:

The FDA review of the SF-12 was based upon the principles delineated in the draft Guidance, “*FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*,” which was published in February 2006. The development of the PRO guidance was based upon the principle that in defining treatment benefit, it is extremely important to determine how a patient feels or functions as a result of treatment, and that the PRO instruments used in clinical trials to determine this benefit need to be appropriate to measure that treatment benefit. The guidance describes how the FDA evaluates PRO instruments when used as efficacy endpoints in clinical trials and provides recommendations for ensuring that these are “fit for purpose” in supporting labeling claims.

The following definitions from the draft FDA PRO Guidance were used in this review:

- **Treatment benefit** is defined as an improvement in how a patient survives, feels, or functions as a result of treatment.
- **Patient-Reported Outcome, or PRO**, is any measurement that is recorded as a direct response by patients without any interpretation by anyone else. A PRO is used to measure any concept that can be known or felt only by the patient (e.g., symptoms).
- **Content validity** of a PRO instrument is evidence that the items and domains of an instrument are appropriate, comprehensive, and interpretable, relative to its intended measurement concept, population and use. Since PRO measurements are designed to capture the patient’s experience, content validity includes patient input and documentation of this input.
- **Health Related Quality of Life (HRQL)** is a concept that represents the patient’s overall perception of the impact of an illness and its treatment. Even though HRQL is a very complex concept, it captures the physical, psychological and social functioning related to the health of the patient, and may be utilized as an efficacy assessment in a clinical trial. **Quality of life (QOL)** instruments are measures of the impact of **all** aspects of life on general well-being including, for example, economic status. Unlike HRQL instruments, QOL instruments are not health-specific and cannot be used to support labeling claims.

PRO INSTRUMENT SUMMARY

In NDA 22-275, the SF-12 was used as a secondary endpoint in studies 156-02-235 and 156-03-238, in order to support the primary efficacy claim of treatment of hyponatremia in patients with nonhypovolemic hyponatremia. A copy of the SF-12 is located in the Appendix.

12-Item Short Form Health Survey (SF-12)

The 36-item short form health survey (SF-36) was developed as a multi-purpose, health status questionnaire. The SF-12 is a 12-item generic measure of overall health status that is composed of a subset of questions from the original SF-36 parent instrument.^{2,3} Version 1 of the instrument, which includes a one-week recall period (Appendix), was administered in the tolvaptan clinical studies as a secondary endpoint.

The SF-12 includes items related to the following areas:

- Physical functioning (2 items)
- Role physical (2 items)
- Bodily pain (1 item)
- General health (1 item)
- Vitality (1 item)
- Social functioning (1 item)
- Role emotional (2 items)
- Mental health (2 items)

There is no single total score for the SF-12, but rather two summary scores. These two summary scores calculated from the SF-12 items are named the Physical Component Score (PCS) and the Mental Component Score (MCS). These summary scores were utilized in the tolvaptan clinical trials to measure mental and physical health status, respectively. The same 12 items from the SF-12 instrument are used to calculate the both the PCS and MCS scores, but these items are weighted differently for each score. Therefore, each summary score includes items that are not directly associated to the concept of interest (e.g., mental summary score includes items regarding bodily pain).

The SF-12 was developed as a multi-purpose health survey. It is not specific to the target population i.e., patients with hyponatremia as were enrolled in the trials. The adequacy of an instrument to define clinically significant treatment effects depends on established content validity in the target population. Content validity is established by demonstration using qualitative research that the items are complete, meaningful, interpretable, and appropriate for patients enrolled in the trials. Content validity of the SF-12 has not been established to represent the impact of hyponatremia on health status, a very general concept that includes all aspects of health. Like health-related quality of life (HRQL), a health status measure would need to capture all of the important subconcepts of health, including physical, social, and psychological aspects.

Content validity concerns arise from a reading of the items in the instrument and finding that some items may not be appropriate for the target population/indication. For example, the item,

“During the past week, how much did pain interfere with your normal work?”, may not show evidence of content validity for the target population, because pain is typically not a symptom of hyponatremia.

Content validity is also questioned by noticing that the SF-12, and SF-36 do not assess what we know to be the main clinically important signs and symptoms of hyponatremia, including nausea, headache, lethargy, and confusion. The PCS and MCS of the SF-12 were included in the tolvaptan clinical trials to measure the treatment effect on physical and mental health status, respectively. However, the major signs and symptoms of hyponatremia for the target population of patients, including the neurocognitive manifestations, are not measured by the SF-12. For example, the MCS includes items about mood and anxiety. However, measures of the relevant and important neurological and cognitive manifestations associated with hyponatremia would have been more appropriate in this patient population.

In addition, due to content validity concerns, it is unclear how to interpret the changes in the SF-12 PCS and MCS summary scores with treatment. As noted above, both the PCS and MCS summary scores include all 12 items of the SF-12 instrument, but with different item weighting. Mental functioning items are included in the PCS and physical functioning items are included in the MCS. Therefore, unless the scoring algorithm is available, it cannot be determined which specific items contributed to the differences in scores between treatment groups.

As of May 21, 2008, information concerning the SF-12 PCS and MCS scoring algorithms had not been submitted by the sponsor. Because a change in score represents a composite of all domains, without this information, it is difficult to describe based upon the MCS and PCS, the outcome achieved with treatment.

CONCLUSIONS:

In summary, as delineated in the draft FDA PRO Guidance, a claim of treatment benefit includes an assessment of the ability of the PRO instrument to measure the claimed concept and is specific to the intended population and to the characteristics of the condition or disease treated. The SF-12 MCS and PCS are generic measures of overall health status and are not measures of the clinically important signs and symptoms associated with hyponatremia, including the neurocognitive manifestations of hyponatremia. The SF-12 MCS and PCS are not appropriate as stand-alone PRO measures to support labeling claims of treatment benefit in patients with hyponatremia.

References:

1. US Food and Drug Administration: Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims. <http://www.fda.gov/cder/guidance/5460dft.pdf>
2. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34(3):220-33
3. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998; 51:1171-8

APPENDIX

SF-12: Version 1, One Week Recall Period

In general, would you say your health is:

- 1 Excellent
- 2 Very good
- 3 Good
- 4 Fair
- 5 Poor

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

- 1 Yes, limited a lot
- 2 Yes, limited a little
- 3 No, not limited at all

Climbing several flights of stairs

- 1 Yes, limited a lot
- 2 Yes, limited a little
- 3 No, not limited at all

During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Accomplished less than you would like

- 1 Yes
- 2 No

Were limited in the kind of work or other activities

- 1 Yes
- 2 No

During the past week, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Accomplished less than you would like

- 1 Yes
- 2 No

Didn't do work or other activities as carefully as usual

- 1 Yes
- 2 No

During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

- 1[] Not at all
- 2[] A little bit
- 3[] Moderately
- 4[] Quite a bit
- 5[] Extremely

These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past week:

Have you felt calm and peaceful?

- 1[] All of the time
- 2[] Most of the time
- 3[] A good bit of the time
- 4[] Some of the time
- 5[] A little of the time
- 6[] None of the time

Did you have a lot of energy?

- 1[] All of the time
- 2[] Most of the time
- 3[] A good bit of the time
- 4[] Some of the time
- 5[] A little of the time
- 6[] None of the time

Have you felt downhearted and blue?

- 1[] All of the time
- 2[] Most of the time
- 3[] A good bit of the time
- 4[] Some of the time
- 5[] A little of the time
- 6[] None of the time

During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1[] All of the time
- 2[] Most of the time
- 3[] Some of the time
- 4[] A little of the time
- 5[] None of the time