Health Care Providers:

1. What is SERVE-HF?

SERVE-HF is a multinational, multi-center, randomized controlled trial designed to assess whether treatment of predominantly Central Sleep Apnea with Adaptive Servo-Ventilation (ASV) therapy reduces mortality and morbidity in patients with chronic heart failure who are receiving optimized medical therapy.

The study recruited a total of 1,325 subjects who were randomized to one of the two arms. The details of the study can be found on https://clinicaltrials.gov/ct2/show/NCT00733343

2. What were results?

Analysis of the study results is ongoing but ResMed has acted swiftly to address this new information. Only the top-line results are available at this time.

We can provide the following data at this time:

Preliminary results have become available for the SERVE-HF trial which assessed the effects of treatment of predominant central sleep apnea with Adaptive Servo-Ventilation (ASV) on mortality and morbidity in patients with symptomatic chronic heart failure with reduced ejection fraction (HFrEF).

The preliminary primary results show no significant difference between patients treated with ASV and those in the control group for the primary endpoint of time to all-cause mortality or unplanned hospitalization for worsening heart failure (based on a hazard ratio [HR] =1.136, 95 percent confidence interval [95% CI] =(0.974, 1.325), p-value= 0.104). However, there is a statistically significant 2.5 percent absolute increased annual risk of cardiovascular mortality for those randomized to ASV therapy compared to the control group. In the study 10.0 percent of the ASV group experienced a cardiovascular death each year compared to 7.5 percent of the control group, representing a 33.5 percent relative increased risk of cardiovascular mortality (HR=1.335, 95%CI=(1.070, 1.666), p-value= 0.010).

3. Who is at risk?

The patient population studied in the SERVE-HF trial is considered at risk for increased cardiac mortality. Specifically, that is patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) (New York Heart Association Classification Levels [NYHA] 2-4) on ASV therapy for predominantly central sleep apnea.

4. Should affected patients discontinue therapy?

ResMed recommends that physicians contact their at risk patients to discuss whether to discontinue treatment given that no benefit was observed in SERVE-HF patients treated with ASV and there was an increased risk of cardiovascular mortality. Whether to discontinue is ultimately a clinical decision.

5. Are the devices malfunctioning?
There has been no malfunction or technical fault observed with the ASV device operation; it operates correctly to treat predominant central sleep apnea.

The increased risk of cardiovascular death occurred in a scientific study (SERVE-HF) investigating the use of ASV therapy in people with moderate to severe predominant central sleep apnea and symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) .

6. How quickly do I have to ask them to stop therapy?
We recommend you urgently contact those patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%)
on ASV therapy to discuss immediate discontinuation of ASV treatment.

7. What do I do now with new patients?
ASV therapy will be contraindicated for patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%).

8. Does the risk change with time on therapy?
Based on our preliminary assessment of the data from SERVE-HF, it appears that the risk for cardiovascular mortality in patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) does not change with time on therapy and is independent of perceived benefit from therapy.

9. Does ASV mode with automatic EPAP have the same issue as the ASV mode with fixed EPAP?
The devices used in the SERVE-HF trial had fixed EPAP but we believe that automatic EPAP may also increase cardiovascular risk in patients with symptomatic chronic heart failure with reduced ejection fraction (LVEF>45%).

10. What about patients with cardiovascular diseases other than heart failure that are using ResMed's ASV therapy. Are they at risk as well?
The results of SERVE-HF cannot be extrapolated to patients with cardiovascular diseases other than heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%). SERVE-HF only investigated patients with symptomatic chronic heart failure patients with reduced EF and predominant central sleep apnea.

11. What about patients suffering from heart failure using continuous positive airway pressure (CPAP or APAP) for Obstructive Sleep Apnea or a ventilation device for respiratory disorders? Are they at risk and should they be concerned?
The results of SERVE-HF cannot be extrapolated to patients treated with CPAP, APAP or any other ventilation device.

12. My heart failure patients have fewer symptoms when using ResMed's ASV device. Does that mean ASV therapy is beneficial and they may be maintained on therapy?

The increased cardiovascular risk shown in SERVE HF is independent of symptomatic improvement. We recommend you urgently contact those patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) on ASV therapy to discuss with them immediate discontinuation of ASV treatment.

For patients who have OSA, the physician may consider transitioning them to CPAP/APAP.

13. What do I do if my heart failure patient does not want to give up on the ASV therapy?

The patient population studied in the SERVE-HF trial is considered at risk for increased cardiac mortality; specifically patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45) on ASV therapy. Because of the increased mortality risk in the affected patient population, ResMed is updating its user guide and clinical manual for its ASV device to add a contraindication for use of this therapy with those patients.

We recommend you urgently contact those patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) currently on ASV therapy to discuss the immediate discontinuation of ASV treatment.

ResMed defers to the clinical judgment of physicians, in consultation with their patients, regarding the proper course of treatment for any particular patient based on that patient's condition, and whether a particular course of treatment should continue to involve ASV therapy
The decision to continue or discontinue therapy is for patients and their physicians to make. However, based on the results of Serve-HF ResMed is updating its user guide and clinical manual for its ASV devices to add a contraindication for use of this therapy.

14. Is therapy with PAP devices safe?

Serve HF has shown that treatment of central sleep apnea with adaptive servo ventilation in patients with chronic heart failure with reduced ejection fraction was associated with an increased risk of cardiovascular mortality. This group of patients is a very small minority (less than 1%) of those using PAP devices. In addition to their use in the treatment of central sleep apnea PAP devices are more commonly used for the treatment of OSA and of respiratory failure. There is no evidence to suggest that the use of PAP devices in these clinical applications is associated with increased risk of cardiovascular events or death.

15. Are there patients that SHOULD stay on ASV?

For patients with central sleep apnea or complex sleep apnea but without symptomatic chronic heart failure and reduced ejection fraction, there is no evidence to suggest that there is increased risk of cardiovascular death.

ResMed's manuals for our ASV products are being updated to contraindicate the use of ASV in patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) Other indications for ASV therapy are unchanged.

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