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Urgent: Field Safety Notice

Increased Risk of Cardiovascular Death with Adaptive Servo-Ventilation (ASV) Therapy For Patients with Symptomatic Chronic Heart Failure with Reduced Ejection Fraction

Date: May 13, 2015

Distribution: Distributors of devices with ASV therapy
Medical and nursing staff in professional health care facilities
Health Care Providers (HCP)

Description of issue:

A serious safety concern has been identified during the preliminary primary data analysis from the SERVE-HF clinical trial. This trial investigated the effect of Adaptive Servo-Ventilation (ASV) therapy on the hospitalization and mortality rate of patients with symptomatic, chronic heart failure (NYHA 2-4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) and moderate to severe predominant central sleep apnea (AHI ≥ 15/h, CAHI/AHI ≥ 50% and CAI ≥ 10/h).

Hazards involved:

The identified safety concern is a significant increase in the risk of cardiovascular death in patients with symptomatic, chronic heart failure (NYHA 2-4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) being treated with Adaptive Servo-Ventilation.

Products affected:

The following ResMed devices are affected:

- VPAP Adapt
- VPAP Adapt SV
- S9 VPAP Adapt
- S9 VPAP Tx
- VPAP Tx
- Lumis Tx
- AirCurve 10 ASV

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Manufacturer:

ResMed Ltd
1 Elizabeth Macarthur Drive
Bella Vista 2153
Australia

Immediate action required:

Physicians managing patients with symptomatic chronic heart failure with reduced ejection fraction who are using ResMed ASV devices should contact their patients to discuss discontinuation of treatment.

Distributors / Suppliers of Medical Devices:

This Safety Notice needs to be provided to all health care providers or physicians who have prescribed ASV therapy, or all health care facilities which have purchased affected products.

Physicians:

The present data raises concerns with respect to patients with symptomatic, chronic heart failure (NYHA 2-4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) who are on ASV therapy. This is the patient population studied in the SERVE-HF trial that is now considered at risk.

- For this at risk population there is a 33.5% increased risk of cardiovascular death, compared to equivalent patients who are not on ASV therapy (absolute annual risk: 10% in ASV patients vs. 7.5% in control group).
- The SERVE-HF study has identified no patient benefit from the use of ASV therapy in the at risk patient group with chronic systolic heart failure.
- New at risk patients should not use ASV. ASV therapy is now contraindicated in these at risk patients.
- Before putting patients on ASV, each patient should be assessed for Heart Failure. In case of signs and symptoms of Heart Failure an objective assessment of LVEF should be performed.
- Physicians need to identify and reassess all patients with symptomatic chronic heart failure with reduced ejection fraction currently being treated with ASV devices with the aim of urgently stopping ASV therapy. The decision about current patients continuing on therapy should be made considering this significant increased risk of death and lack of observed patient benefit, and also considering:

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- The increased cardiovascular mortality is mainly attributed to death occurring out of hospital (likely "sudden cardiac death")
- Deaths attributed to use of this therapy may often occur without a preceding hospitalization or worsening symptoms
- The risk does not reduce with time on therapy
- The risk should be considered independent of perceived patient response to therapy

There has been no malfunction or technical fault with the operation of the device, it operates correctly to treat central sleep apnea. The identified risk is with the use of ASV in this identified at risk population.

Distributors, health care providers or medical staff who have questions about this Safety Notice should:

- Call the SERVE-HF Safety Notice Center at 1 (800) 478-9010 from the U.S. and Canada or at +1 (858) 836-5200 from outside the U.S. and Canada
- Go to SERVE-HFfaqs.com for more information including answers to frequently asked questions
- Contact their ResMed representative

ResMed's primary focus is to provide safe and effective therapy for our patients. The SERVE-HF trial was initiated to understand the effect of ASV therapy in heart failure patients. As the preliminary data have identified an unexpected safety concern, we consider this urgent Safety Notice as necessary to enable physicians to reassess the use of ASV therapy in heart failure patients as soon as possible.

Yours truly,

Lionel King
Senior Vice President Global Quality Assurance and Regulatory Affairs

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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.

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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.

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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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Country	Hotline #
United States	1-800-478-9010
France	0805408804
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Germany	0800 2770400
Austria	+49 89 9901 0565
Sweden	+46 8477 10 00
Switzerland	0800 00 25 00
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Portugal	+33805408804
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PHILIPS

May 15, 2015

Philips Sleep and Respiratory Care Statement – ResMed ASV Clinical Trial Announcement

On May 13, 2015 ResMed issued a press release and a related Urgent Field Safety Notice. This report described a statistically significant 2.5 percent absolute increased annual risk of cardiovascular mortality for those randomized to a ResMed adaptive servo ventilation (ASV) therapy compared to the control group. In the patient population with LVEF ≤ 45%, 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).

Philips is actively evaluating the information provided by ResMed and examining if this might impact the medical care of patients who use Philips BiPAP autoSV/BiPAP autoSV Advanced devices. As part of this ongoing investigation, we are working with ResMed in order to better understand their study data. We are also evaluating post market surveillance data, public adverse event data and other published data to identify and assess other safety concerns that may be present.

Until we complete our investigation, based on the ResMed data, we strongly recommend clinicians to adhere to the recommendations that have been published by ResMed and by regulatory authorities cautioning against the use of ASV therapy in patients with symptomatic chronic heart failure (NYHA 2-4) and reduced LVEF≤45%, AND moderate to severe predominant central sleep apnea. ResMed is advising physicians prescribing ASV therapy to not place new patients in the at-risk population on the devices and to evaluate current patients; a discussion about whether to discontinue ASV therapy should occur if a current patient is found to be in the at-risk population. Therefore, as a precaution, physicians should assess individual risks before prescribing BiPAP autoSV/BiPAP autoSV Advanced therapy for the at-risk patient population. No other patient populations have been identified as at-risk for adverse outcomes.

Philips Respironics BiPAP autoSV/BiPAP autoSV Advanced devices are currently indicated to provide non-invasive ventilatory support to adult patients (>30 kg/66 lbs.) with obstructive sleep apnea and respiratory insufficiency caused by central and/or mixed apneas and periodic breathing. These devices are not approved or labeled for the treatment of heart failure.

We will continue to provide updates to the medical and service provider communities as additional information becomes available to ensure the continuous safe and effective use of our devices.

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NOTE: Please forward all **media and analyst** queries, without comment, to Mario Fante in Philips Healthcare PR: mario.fante@philips.com, 603-560-9226.