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Philips Respironics

Response to the ResMed SERVE-HF Trial Results

Field Safety Notification

Use of auto servo ventilation (ASV) devices on patients with symptomatic chronic heart failure (NYHA 2-4) and reduced LVEF≤45%, AND moderate to severe predominant central sleep apnea

BiPAP autoSV Advanced System One (60 Series, 30 cm)
BiPAP autoSV Advanced System One (60 Series)
BiPAP autoSV Advanced System One (50 Series)
BiPAP autoSV Advanced w/SmartCard (SV3)
BiPAP autoSV w/SmartCard (SV2)
OmniLab Advanced +
OmniLab Advanced
BiPAP autoSV
HeartPAP

Dear Customer,

This document contains important information for the continued safe and proper use of your equipment.

Please review the following information with all members of your staff who need to be aware of the contents of this communication. It is important to understand the implications of this communication.

Please retain a copy with the equipment Instruction for Use.

ResMed has issued an Urgent Field Safety Notice that 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 the Philips devices listed above. Until we complete our investigation, based on the ResMed announcement, we strongly recommend clinicians adhere to the following recommendations.

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Do not place new patients with symptomatic chronic heart failure (NYHA 2-4) and reduced LVEF≤45%, AND moderate to severe predominant central sleep apnea on ASV therapy. 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. Current patients should be evaluated and a discussion about whether to discontinue ASV therapy should occur if a current patient is found to be in the at-risk population.

If it is unknown whether a current patient falls within the at-risk population, the patient should be evaluated to determine if ASV therapy should continue.

No other patient populations have been identified as at-risk for adverse outcomes.

Philips has issued a press release alerting the healthcare community of this issue.

Should you have any questions or need further information regarding this communication, please do not hesitate to contact your local Philips representative.

This notice has been reported to the appropriate Regulatory Agency.

Philips apologizes for any inconveniences caused by these recommendations.

Sincerely,

Jonathan W. Demarest
Head of Quality & Regulatory, SRC, Philips

For media and analyst inquiries, please contact Mario Fante in Philips Healthcare at mario.fante@philips.com, or by phone at 1-603-560-9226.

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FAQs

What is a Field Safety Notification?
A Field Safety Notification (FSN) is a worldwide communication that medical device manufacturers use to inform their customers of actions the manufacturer and customer must take to manage safety-related risks the manufacturer becomes aware of after the product has been released to the field. The process of issuing an FSN is governed by local regulatory authorities.

What does this Field Safety Notice involve?
This FSN informs customers of the preliminary findings of the ResMed SERVE-HF study as they relate to autoSV in Philips Respironics devices and provides recommendations to consider before using or if using the BiPAP autoSV or OmniLab devices (complete device list is above).

Is this a device recall?
No. The devices are operating properly and as designed and may continue to be used safely as directed with consideration of the advisory in the FSN.

What patients are at risk? What is the 'sub-group'?
Patients with symptomatic chronic heart failure (NYHA 2-4), reduced LVEF≤45%, AND moderate to severe predominant central sleep apnea are the identified sub-group at risk.

Should new patients be placed on BiPAP autoSV Advanced and OmniLab devices identified in the Field Safety Notice?
At this time, and until further investigation is completed, Philips Respironics is advising that new patients with symptomatic chronic heart failure (NYHA 2-4), reduced LVEF≤45%, AND moderate to severe predominant central sleep apnea are not placed on the identified devices.

Before putting patients on an identified device, 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.

Any other patients that are covered in the Intended Use of this therapy device, can be safely considered for a BiPAP autoSV Advanced prescription, as they are NOT included in the ResMed SERVE-HF results.

What should be done with current patients on BiPAP autoSV Advanced devices?
Current patients should be evaluated and a discussion about whether to discontinue BiPAP autoSV therapy should occur if a current patient is found to be in the at-risk population.

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What should I do if I am a patient?
If you are a current patient on a BiPAP autoSV device, you should contact your health care professional and discuss if you may be in the effected sub-group and determine the appropriate course of action for you.

What should I do if I am a distributor?
As a precaution, physicians should assess individual risks before prescribing therapy with the Philips devices listed above for the at-risk patient population. No other patient populations have been identified as at-risk for adverse outcomes.

Based on this, customers (including DMEs, distributors and other organizations that have purchased one of the identified devices) should contact the prescribing physician and/or the patient and alert them about this situation.

If I am a distributor, can I get a list of serial numbers for devices purchased by my organization?
Yes, please contact your local Philips organization to request serial numbers.

What should I do if I am a physician?
As a precaution, physicians should assess individual risks before prescribing therapy with the Philips devices listed above for the at-risk patient population. No other patient populations have been identified as at-risk for adverse outcomes. Additionally, current patients should be evaluated and a discussion about whether to discontinue BiPAP autoSV therapy should occur if a current patient is found to be in the at-risk population.

What are the risks of halting treatment in patients with HF who seemingly are responding positively to ASV? What device modality should these patients be switched to?
This is a determination that can only be made by a patient's physician.

Were Philips Respironics devices used in the ResMed SERVE-HF study?
No, Philips Respironics devices were not used in the ResMed SERVE-HF study.

Is there a trial to investigate the effectiveness of the Philips Respironics BiPAP autoSV Advanced on Heart Failure patients?
Yes. The ADVENT-HF trial is an investigator-initiated trial that is jointly funded by a peer-reviewed grant from the Canadian Institutes of Health Research and an unrestricted grant from Philips Respironics. Dr. Douglas Bradley is the study's principal investigator.

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What is the aim of the ADVENT-HF study?

The primary outcome of the ADVENT-HF study is the composite endpoint of death, cardiovascular hospitalizations, appropriate discharges from an ICD (implantable cardioverter defibrillator), and new onset atrial fibrillation/flutter requiring anti-coagulation. Endpoint is 540 primary events.

What is the status of the ADVENT-HF trial? Do they continue to recruit patients?

At a special meeting on May 18, 2015, following ResMed's announcement of the preliminary results of the ResMed SERVE-HF trial, the Data Safety Monitoring Board (DSMB) of ADVENT-HF reviewed the interim data of 308 HF patients that were segregated into those with Central Sleep Apnea (CSA) and those with Obstructive Sleep Apnea (OSA), and reported that no safety signal was observed in either group. They therefore recommended that the trial continue without changes to the current protocol and that both obstructive sleep apnea (OSA) and central sleep apnea (CSA) patients could continue to be enrolled. The trial is currently recruiting patients.

Is there any data released from the ADVENT trial that provides additional insight into the use of ASV therapy in heart failure patients?

Much of the earlier research conducted on ASV by medical experts has shown beneficial outcomes and minimal adverse effects.[1] These early reports were the basis for larger scale research, including "Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure" (ADVENT-HF), and SERVE-HF. ADVENT-HF is an investigator-initiated trial that is jointly funded by a peer-reviewed grant from the Canadian Institutes of Health Research and an unrestricted grant from Philips Respironics.

The study includes adults with HF (LVEF ≤ 45%) on optimal therapy, and AHI ≥ 15 (OSA and CSA) randomized to ASV or controls. In the ADVENT-HF trial, 318 patients have been randomized to controls or the BiPAP autoSV device as of June 1, 2015. At a special meeting on May 18, 2015, the Date Safety Monitoring Board (DSMB) of ADVENT-HF reviewed the interim data of 308 patients that were segregated into those with CSA and those with OSA and reported that no safety signal was observed in either group. They therefore recommended that the trial continue without alteration to the protocol and that both OSA and CSA patients could continue to be enrolled.

What is the current Indication for Use of the Philips Respironics BiPAP autoSV Advanced?

The BiPAP autoSV Advanced System One is intended to provide non-invasive ventilatory support to treat adult patients (>30 kg/66 lbs.) with Obstructive Sleep Apnea and Respiratory Insufficiency caused by central and/or mixed apneas and periodic breathing. This device may be used in the hospital or home.

These devices are not cleared or labeled for the treatment of Heart Failure.

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[1] *See Tables below.*

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What patients can be placed on the Philips Respironics BiPAP autoSV Advanced devices?
According to the Intended Use of the BiPAP autoSV Advanced device, patients that fall within the intended use can still be placed on the device, although the risks identified for the at-risk population identified in the Field Safety Notice should be considered when doing so.

Will you change the labeling or manuals for the Philips Respironics BiPAP autoSV Advanced and OmniLab devices?
Philips continues to evaluate information from the ResMed SERVE-HF study. This is a complex analysis because the study was not done using Philips devices, making understanding how the study data applies to Philips devices challenging. Once more information is obtained and further analysis completed, Philips Respironics will communicate its final determination on our devices' labeling to continue to ensure the safety of patients that use these devices.

Does the Philips Respironics BiPAP autoSV Advanced have a contraindication at this time?
At this time, the Philips Respironics BiPAP autoSV Advanced devices are not contraindicated for the at-risk population. While we investigate the issue, we have informed and cautioned customers about the ResMed SERVE-HF preliminary results with respect to Philips Respironics devices. We are committed to determining the best long-term solution for this issue to continue to assure patient safety.

Does this effect Philips Respironics and ResMed devices?
Although this was a ResMed study, and no Philips Respironics devices were used in the study, Philips Respironics is proceeding with utmost caution until more information is available, and advising the health care community to follow the ResMed advice on the subgroup population.

As more information becomes available on the differences between the use of the ResMed ASV device and the use of the Philips Respironics BiPAP autoSV Advanced device, we will make the information available and take appropriate action.

What is ASV / autoSV therapy? What is the difference between ResMed and Philips devices with this functionality?
Servo-ventilation devices monitor airflow patterns then deliver varying pressure levels during inhalation and exhalation in an attempt to resolve complex breathing (periodic) patterns.

The primary differences between the ResMed ASV and the Philips autoSV and autoSV Advanced devices are related to the proprietary algorithms of each device, which monitor and detect periodic breathing, and deliver pressure support levels and response timing. This functionality on our devices is similar, but NOT identical to the ResMed ASV functionality.

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Is the BiPAP with Bi-Flex also included in this advisory?
Only devices with the autoSV mode are included in this advisory. The BiPAP Auto does not deliver the servo-ventilation (autoSV) mode, so it is not affected by this Field Safety Notification.

For guidance on the devices that are subject to the Field Safety Notification, please see the list of devices at the top of this page.

Does this caution apply to other Philips Respironics PAP devices?
This caution applies only to servo-ventilation devices, so this advice only applies to the devices listed in the Field Safety Notice and only to patients in the specific sub-group described previously.

Is the autoSV device working properly?
The BiPAP autoSV and BiPAP autoSV Advanced algorithms are working correctly, and their efficacy has been previously validated.

Are Philips Respironics sleep devices with autoSV functionality in danger of malfunctioning?
No. At this time there is no indication of performance issues leading to safety risks in Philips Respironics sleep devices with autoSV functionality.

I ordered a BiPAP autoSV Advanced device, but they were not available for sale, why? Did you detect an operating problem?
Philips decided to temporarily suspend shipments of the BiPAP autoSV Advanced and the OmniLab Advanced + devices when this information was first available to determine the impact of the results of the ResMed SERVE-HF study. This is standard procedure in matters of medical devices under the applicable regulatory obligations. This decision was not the result of a technical malfunction or product failure, but is due to the communication of preliminary results of the ResMed SERVE-HF study.

We are now shipping devices to countries worldwide.

When will you have more information?
Philips continues to evaluate the information. This is a complex situation and should not be rushed into. Philips Respironics has dedicated resources looking into the situation who are highly skilled in this area. This is not a Philips Respironics study. It is our responsibility to determine the right course of action with respect to our products.

Further communication will follow when the investigation is complete and at that time the going forward plan will be determined and communicated.

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When does Philips expect to have conclusions from the investigation it is conducting?
Philips Respironics continues to actively evaluate the information provided by the SERVE-HF trial published on September 1, 2015 in the New England Journal of Medicine. It remains unclear whether the effects seen in the SERVE-HF trial are specific to only the ResMed devices used in the trial, or applicable to all ASV therapies, as there are differences in algorithms among the different ASV devices.

Philips Respironics will continue to seek to work with ResMed to clarify some important points related to data collection and analysis by the SERVE-HF trial investigators that have been raised by clinicians and researchers, specifically the analysis of harm based on "intent to treat" or "as treated" data as recommended by scientists and biostatisticians[2], the dose-response of outcomes and risks based on actual hours of device use, and the threshold of LVEF that was related to the harm from ASV therapy. An understanding of these key issues would allow the medical community to better assess autoSV therapy options for the population identified in the ResMed study.

While we continue to analyze the data from the ResMed SERVE-HF trial and the results of the ADVENT-HF trial (a trial sponsored by Philips Respironics utilizing Philips Respironics autoSV devices to help to better define the role of autoSV in the treatment of patients with sleep disordered breathing and heart failure), we maintain our current recommendation to adhere to the guidance concerning the ResMed SERVE-HF trial.

Why did Philips Respironics issue a Field Safety Notification (FSN) if you are still investigating?
In the utmost of caution, Philips issued the Field Safety Notification based on the preliminary analysis of the ResMed SERVE-HF data provided by ResMed. Because of the increased mortality noted in the Adaptive Servo Ventilation therapy arm of their study and the lack of understanding of the contributing mechanism, Respironics felt that providing to customers, prescribers and patients was necessary to ensure they had sufficient information to make appropriate decisions on managing their health.

[2] *Detry MA, Lewis RJ. JAMA Guide to statistics and methods. The intention-to-treat principle. How to assess the true effect of choosing a medical treatment. JAMA. 2014; 312: 85-86.*

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Table 1: Performance of Philips Respironics BiPAP autoSV in treating Sleep Disordered Breathing in Heart Failure

Peer reviewed publication reference	Severity of SDB, AHI, baseline or no treatment	Severity of SDB, AHI, treated with autoSV	p-value (vs. no treatment)
Kasai T, et al. 2013[1] *Adaptive servo-ventilation in cardiac function and neurohormonal status in patients with heart failure and central sleep apnea nonresponsive to continuous positive airway pressure.*	25.0 ± 6.9 (on CPAP)	2.0 ± 1.4	**< 0.001**
Kasai T, et al. 2010[2] *Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration.*	36.3 ± 19.4	1.9 ± 2.1	**< 0.01**

Table 2: Performance of Philips Respironics BiPAP autoSV in treating Obstructive Apnea in Heart Failure

Peer reviewed publication reference	Obstructive Apnea Index (OAI), no treatment	OAI treated with autoSV	p-value (vs. no treatment)
Javaheri S, et al. 2011[3] *The performance of two automatic servo-ventilation devices in the treatment of central sleep apnea.*	12 ± 17	1 ± 2	**< 0.001**
Yoshihisa A, et al. 2011[4] *Adaptive servo ventilation improves cardiac dysfunction and prognosis in chronic heart failure patients with Cheyne-Stokes respiration.*	2.3 ± 3.7	1.0 ± 2.1	0.09
Miyata M, et al. 2012[5] *Adaptive servo ventilation improves Cheyne-Stokes respiration, cardiac function, and prognosis in chronic heart failure patients with cardiac resynchronization therapy.*	1.3 ± 3.0	0.5 ± 1.3	0.07
Javaheri S, et al. 2015[6] *The use of a fully automated automatic adaptive servoventilation algorithm in the acute and chronic treatment of central sleep apnea.*	17 ± 17	1 ± 2	**< 0.001**
Suzuki S, et al. 2014[7] *Adaptive servo-ventilation therapy improves long-term prognosis in heart failure patients with anemia and sleep-disordered breathing.*	HF + anemia 3.3 ± 6.4	HF + anemia 0.9 ± 1.6**	HF + anemia 0.0833
	HF + no anemia 2.7 ± 5.8	HF + no anemia 0.8 ± 1.4**	HF + no anemia 0.1478
Randerath WJ, et al. 2012[8] *Long-term auto-servoventilation or constant positive pressure in heart failure and coexisting central with obstructive sleep apnea.*	11.6 ± 10.2	2.3 ± 4.9* 4.6 ± 6.9 ***	**< 0.001**

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Table 3: Performance of Philips Respironics BiPAP autoSV in treating Central Sleep Apnea in Heart Failure

Peer reviewed publication reference	Central Apnea Index (CAI), no treatment	CAI treated with autoSV	p-value (vs. no treatment)
Miyata M, et al. 2012[5] *Adaptive servo ventilation improves Cheyne-Stokes respiration, cardiac function, and prognosis in chronic heart failure patients with cardiac resynchronization therapy*	14.8 ± 13.6	0.6 ± 1.5	**< 0.01**
Arzt M, et al. 2008[9] *Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure.*	32 ± 5	1 ± 0	**< 0.001**
Randerath WJ, et al. 2008[10] *Adaptive servo-ventilation in patients with coexisting obstructive sleep apnoea/hypopnoea and Cheyne-Stokes respiration.*	33.1 ± 10.8	6.1 ± 5.9	**< 0.01**
Randerath WJ, et al. 2012[8] *Long-term auto-servoventilation or constant positive pressure in heart failure and coexisting central with obstructive sleep apnea.*	23.1 ± 13.2	6.1 ± 7.8 (12 mo.)	**< 0.01**
Yoshihisa A, et al. 2011[4] *Adaptive servo ventilation improves cardiac dysfunction and prognosis in chronic heart failure patients with Cheyne-Stokes respiration.*	19.5 ± 14	1.6 ± 2.1	**< 0.01**
Javaheri S, et al. 2011[3] *The performance of two automatic servo-ventilation devices in the treatment of central sleep apnea.*	16 ± 19	3 ± 4 with autoSV 0.6 ± 1 with autoSV Advanced	**< 0.001**

For media and analyst inquiries, please contact Mario Fante in Philips Healthcare at mario.fante@philips.com, or by phone at 1-603-560-9226.

About Royal Philips:

Royal Philips (NYSE: PHG, AEX: PHIA) is a diversified health and well-being company, focused on improving people's lives through meaningful innovation in the areas of Healthcare, Consumer Lifestyle and Lighting. Headquartered in the Netherlands, Philips posted 2014 sales of EUR 21.4 billion and employs approximately 108,000 employees with sales and services in more than 100 countries. The company is a leader in cardiac care, acute care and home healthcare, energy efficient lighting solutions and new lighting applications, as well as male shaving and grooming and oral healthcare. News from Philips is located at www.philips.com/newscenter.