1. The medical device ´AlaxoStent´

The product bears the CE Mark and therefore is a medical device approved in the EU. It is not yet FDA approved as a medical device for the US. Availability in countries outside of Europe has to be checked for each country.

Approval as a medical device does not mean automatic reimbursement by public or private health insurance in Germany or other countries. The AlaxoStent is a prescription device.

2. Indications for application of the AlaxoStent

- The AlaxoStent is clinically tested for treatment of obstructive sleep apnea (OSA) or ronchopathy. Applicability of the AlaxoStent therapy has to be tested for each individual patient.
- The AlaxoStent must not be used in case of inappropriate structure of the nasal passages, especially if these lead to problems during insertion of the introduction tube into the nasal passage. Patients suffering from a hole in the nasal septum and similar anatomical disorders may not be accessible to treatment with the AlaxoStent.
- The AlaxoStent is not applicable for treatment of central apneas.
- The AlaxoStent shall not be used by persons with reduced mental ability, with reduced motor skills, with psychic restrictions, mental disorders or spastic syndromes.
- In case of known lung diseases a pneumologic medical examination is required to evaluate if the AlaxoStent therapy can be applied to the specific patient.

3. Mode of action

The AlaxoStent by its opening force in the distal widened section ("tulip") effects a mechanical splinting of the airway in the throat. The opening force is present only in the tulip (left in the image), not in the other section ("shaft braid") of the stent which is positioned in the nasal passage. Concluding, the AlaxoStent cannot splint the nasal passage.

Should a decreased nasal breathing be prevalent the product ´AlaxoLito Nasal Stent´ can be used for splinting of the nasal passage, also in parallel to the AlaxoStent. The AlaxoLito stent exerts its therapeutic effect at the nasal alar and in the lower or middle nasal passage.
The opening force of the AlaxoStent is dimensioned so that an optimal balance between efficacy and tolerance is provided. Nevertheless, it may occur that the opening force is not sufficient for all patients.

The tulip must be positioned at those places in the airway where the obstructions occur in order to provide the opening force there. Especially if obstructions occur outside of the tulip no sufficient therapeutic effect can be achieved because the shaft braid cannot splint such obstructions. The length of the 40 mm tulip is designed so that for standard anatomies the full length of the velopharyngeal and oropharyngeal obstructions are covered. The application for treatment of an epiglottis collapse („floppy epiglottis“) probably will be tolerated only by few patients.

The AlaxoStent is provided in two different total lengths in order to allow optimal adaptation to the different anatomies (length of the nasal passage, height of the pharynx) and the possible higher or deeper positioning in the pharynx:

- AlaxoStent S40 and S30 are the shorter product variants
- AlaxoStent L40 and N30 are the longer product variants

The product variants with the 30 mm long tulip (S30, N30) are not offered in all countries. The product variants with the 40 mm long tulip (S40, L40) enable safe splinting of the airway obstructions also in case of extended collapses or of multiple locations of obstructions.

4. Handling of the AlaxoStent

Components of the AlaxoStent:
1) Self-expanding nitinol braid [1] with clip lock [1a]
2) Pusher [2] with clip lock (the end with the two holes) [2a]
3) Introduction tube [3]
4) Cleaning tube [4]
5) Not shown: Fixation tape
6) Not shown: cleaning spray (Prontosan® Wound Spray)

The AlaxoStent is self-inserted by the patient in the evening and removed in the morning.
The nitinol braid is connected to the pusher [2] by fitting into each other the two parts [1a] and [2a] of the clip lock.

The other end of the pusher [2b] is inserted into the black end [3a] of the introduction tube [3] and the pusher is moved through the introduction tube. Then the nitinol braid is carefully and completely pulled into the introduction tube using the pusher whereby it self-compresses. The clip lock shall be located in the introduction tube and the end of the stent next to the black end.

The introduction tube is carefully introduced with the black end ahead into one nasal passage and advanced horizontally down to the pharynx to its target position (see Section 6A). Only one stent is introduced in one nostril.

In case of dry mucosal tissue in the nose increased friction may result. In such cases a nasal spray containing sea salt, dexamethasone and/or hyaluronic acid may be horizontally sprayed into the nasal passage. Then the introduction tube smoothly moves forward with low friction along the wet mucosal tissue.

The AlaxoStent is suitable for repeated use up to 18 hours per application by patients of age of 18 years and higher.

5. Preparatory examinations

For application of the AlaxoStent patency of at least one nasal passage for the introduction tube (diameter 4 mm) is a requirement. Therefore a medical examination of the nasal passages, especially for the presence of obstructive septum deviations or other anomalies is recommended. This examination can be done e.g. with a standard endoscope. As long as this can be advanced through the full length of the lower or middle nasal passage through to the nasopharynx also the introduction tube should be advanceable without problems. Furthermore, in the naso/velopharynx potentially other anatomical structures, e.g. adenoids, may be present which may hinder introduction of the AlaxoStent. An ORL examination – as recommended in the respective sleep medical guidelines – should be performed before first application.
A preparatory examination for specially high gag reflex sensitivity may be done, too. As described in Section 6C also highly sensitive patients can be efficiently trained to easily apply the AlaxoStent.

Knowledge about the concrete locations of obstructions occurring in a given patient is highly valuable for selection of the optimal OSA therapy in order to be able to suggest the optimal therapy options. Besides endoscopic examinations and ENT mirror exams primarily diagnostic methods such as the ApneaGraph (MRA Medical Ltd.) for an initial topodiagnostic differentiation of „upper“ (velopharyngeal) and „lower“ (hypopharyngeal) obstructions or propofol sleep video endoscopy (PSE) – which allows precise determination of the obstructions – are applicable.

With the ApneaGraph, by recording of the airflow in combination with a differential pressure management at two different positions in the pharynx, presence of a tongue base collapse or an epiglottis collapse can be determined. Thereby, with a relatively simple means, a prediction can be made for the appropriate position of the AlaxoStent to be tested with a given patient (see Section 6A).

By PSE during a short-time artificial sleep the locations of obstructions are visually determined with a video endoscope. By that means an exact and reliable diagnostics and differentiation is possible (see Section 6B).

Another appropriate but relatively new method for determination of the locations of obstructions is imaging of the airways in Digital Volume Tomography (DVT) under propofol. By sliced imaging a three-dimensional image is generated without the video endoscope significantly reducing the free diameter of a nasal passage or the AlaxoStent lumen.

Selection of the most useful diagnostic methods for determination of the locations of obstructions for a given patient resides with the attending physician.

6. Application testing and therapy control

It is foreseen to carry out therapy testing with the patient by using an AlaxoStent sample set. This concurrently allows the patient to develop the subjective feeling for acceptance of the therapy. Possible methods for therapy control are described in the following. The sample stent has to be refurbished by disinfectant cleaning according to the provisions in the ´Information for Physicians´ so that it can be used for testing with different patients.

According to experience there are patients who immediately fully tolerate the AlaxoStent during the first application, and such who experience a gag reflex problem. The critical factor is the instant when the stent braid self-expands and attaches to the pharyngeal wall. Another sensitive area can be the upper soft palate, especially contact by the intro tube. For positioning at the upper tongue base the initial sensitivity of the tongue base has to be considered.

Hereinafter the recommended procedure for therapy testing and – as far as necessary – for training of tolerance in a familiarization phase is described.
A) Positioning of the AlaxoStent:

The most frequently used position of the AlaxoStent is that at the velum and uvula ("soft palate position", arrow in the upper image). Should a diagnosed tongue base collapse be prevalent it may be required to position the AlaxoStent deeper at the upper tongue base ("tongue base position", arrow in lower image) in order to achieve successful therapy.

If a propofol sleep video endoscopy (PSE) is carried out the optimal position of the stent can be easily determined visually during the procedure (see Section 6B).

Otherwise efficacy of the soft palate position shall be examined in a polygraphy. Should the result not be satisfying the tongue base position shall be tested for a better result.

The best means for control for correct positioning by the patient himself is the number of fingers used for holding the introduction tube, measured from the outer end of the tube all the way to the nose. The introduction tube is advanced no further and then retracted. The same holds true for the length of the stent protruding from the nose as a means of control, i.e. the stent protruding about to the upper lip, the lower lip or the chin. Usually the patient quickly develops a feeling and sensitivity for the position of the open end of the stent in the throat. Therefore, it is important to train the patient well in the correct use of the stent so that he is able to safely apply it. The ‘AlaxoStent Head’ graphics (facing page) is intended for patient training.

The stent is fixed at the upper lip, the cheek or the nose with a fixation tape (3M Micropore) and thereby secured against slipping out of position. The tape once must be tightly pressed on the stent braid for secure adhesion.
B) First application during propofol sleep video endoscopy:

If a PSE is carried out for diagnostic purposes in order to localize the positions of obstructions finally the AlaxoStent is introduced to the positions of obstructions and maintenance of patency of the airway is examined. By slight shifting of the stent upwards and downwards the optimal position is determined.

Should a sleep laboratory night be performed at the same day the AlaxoStent may be left in its position until the end of the polysomnography in the morning.

The best procedure for first application is having the patient waking up from propofol sleep with the positioned AlaxoStent. In that way an immediate adaptation to the foreign body sensation in the throat (which is perceived by some patients as low, by others as stronger) is achieved.

C) First application while awake:

Dependent on the request and the characteristic of the patient first application while awake shall be done by the patient himself with active help of the attending physician or by the physician himself. As experienced in each case it is recommended that the physician performs expansion of the stent at the target position by slow retraction of the introduction tube so that the stent is positioned at the correct location. The physician by viewing into the mouth of the patient easily can control the right position.
In the tongue base position the stent – when disappearing behind the tongue – is no deeper introduced than a further 1.5 cm.

Should there arise a too strong gag reflex during release of the stent from the introduction tube which the patient does not overcome, then another introduction test shall be performed with a 2% lidocaine gel (as long as there is no contraindication for the use of lidocaine). Lidocaine gel can also be directly applied as a preventive means for highly sensitive patients. A small amount of lidocaine gel is applied to the outside of the anterior section of the introduction tube. In addition a small amount is applied to the opened tulip of the stent which then is dragged into the introduction tube.

The tube is introduced through the lower or middle nasal passage into the pharynx. There the remaining lidocaine gel on the tube is spread on the pharyngeal wall by moving the tube around. After a short exposure time (about 3-5 minutes) the introduction tube is retracted at the target position (soft palate or tongue base position) and the stent is released. Thereby, the initial reflex which may arise during the stent attaching to the pharyngeal wall, is circumvented. Sleeping with the stent quickly leads to adaptation to the foreign body and to tolerance formation, also during opening of the stent. If necessary the stent initially can be worn for only one or half an hour whereas the wearing time is continuously increased from day to day until sleeping with the stent has become routine. According to experience a few applications only of lidocaine gel and nightly sleeping with the AlaxoStent – ideally only one night – are sufficient to form tolerance to the AlaxoStent.

Introduction of the tube through the nasal passage into the pharynx may – if required – be simplified by tilting the head slightly back.

**D) Therapy control by poly(somno)graphy:**

Therapeutic efficacy of the AlaxoStent shall – potentially after a familiarization phase – be controlled by polygraphy or polysomnography. Only once a good therapeutic result has been achieved the AlaxoStent therapy shall be recommended to the patient.

**E) Therapy control by Digital Volume Tomography (DVT):**

In difficult cases therapy control may be executed by using DVT. This may apply e.g. if the reduction of the free lumen in the nasal passage by the endoscope during PSE conditions a significant decrease of nasal flow, leading to false-negative results due to the resulting partial vacuum in the pharynx. In the tomographic images the unaffected status of the airways is represented. Concurrently measurements can be taken in these images.

(Prof. Dr. Hans-Jürgen Wilhelm, ENT Office Frankfurt-Sachsenhausen, Germany)
F) Potential sources of problems during insertion of the AlaxoStent:

It is important to apply the introduction tube about horizontally into the nasal passage. When introduced too much vertically the upper nasal passage may be targeted. The latter is not suitable for passage of the tube. The introduction tube must be advanced through the lower or middle nasal passage.

During release of the stent a typical human reflex is not to retract the introduction tube from the nose but to advance the stent downwards and thereby to reach the epiglottis. This mostly leads to a gag reflex. It is important to fix the white pusher with one hand in a stable position (e.g. by attaching the elbow to the chest) during retraction of the tube with the other hand.

Similarly, the patient has to be instructed not to introduce the stent at home too deeply but to fix it with the fixation tape in the correct position. This shall avoid slipping of the stent up or down away from the target position due to movement of the soft palate and/or swallowing.

Should the patient be very scared of the first application visually covering the introduction tube so that the patient does not recognize advancement of the tube may be psychologically advantageous.

7. Cleaning of the AlaxoStent

The AlaxoStent after use is slowly retracted from the nose. Cleaning is done under flowing lukewarm (not hot) drinking water. In the second step the stent is pushed over the cleaning tube and further mechanically cleaned under flowing water. Cleaning may only be done longitudinally, never in cross direction.

Subsequently the stent is cautiously pushed off the cleaning tube with the thumb and one finger without exerting any pressure from the lower end to the upper end.

The accessory parts are cleaned in the same way under flowing water. Finally, the AlaxoStent and the accessory parts are sprayed with the cleaning spray which has to act for 1 minute. Then rinse
once more under flowing water and spray again. Regarding the modified steps for disinfectant cleaning in the physician´s office please consult the instructions in the „Information for Physicians“.

8. Clinical studies with the AlaxoStent

The AlaxoStent manifoldy has been tested for its efficacy. The first clinical study with an AlaxoStent with 30 mm long tulip has been carried out in 2007/2008 by Dr. Michael Hartl, at that time the head of the sleep laboratory at the ENT Clinic of the Erlangen University Hospital (Germany). The target of this study was generally testing the therapeutic efficacy of the AlaxoStent and its acceptance by the patients. The participants in the study were diagnosed OSA patients with a mean BMI of 30 who successfully used CPAP for a longer time and well accepted the therapy. After a testing phase under medical supervision the stent was positioned in the tongue base position. In the sleep lab comparative data were gathered from polysomnography during the first night without therapy, the second night with CPAP and the third night with AlaxoStent.

The AlaxoStent reduced the number of obstructive apneas as efficiently as CPAP therapy. Also hypopneas were significantly reduced to almost completely abolished but dependent on the individual patient. Suboptimal reduction of the hypopneas with some patients at that time was attributed to a potentially insufficient opening force of the stent braid for these patients. According to current knowledge it is more probable that the length of the widened section (tulip) when positioned at the upper tongue base was not sufficient for these patients to splint their obstructions also in the upper velopharynx or nasopharynx, resp. This problem now has been solved with the 40 mm long tulip. Furthermore, one of the patients developed central apneas under therapy but was nevertheless included in data evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Without therapy</th>
<th>With AlaxoStent</th>
<th>With CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHI</strong></td>
<td>31/h</td>
<td>19/h</td>
<td>8.2/h</td>
</tr>
<tr>
<td><strong>Number of obstructive apneas</strong></td>
<td><strong>43.0</strong></td>
<td><strong>2.2</strong></td>
<td><strong>2.5</strong></td>
</tr>
<tr>
<td><strong>Number of obstructive hypopneas</strong></td>
<td>120</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td><strong>Mean oxygen saturation</strong></td>
<td>92%</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Minimal oxygen saturation</strong></td>
<td>79%</td>
<td>84%</td>
<td>89%</td>
</tr>
</tbody>
</table>

*Results of the first clinical study (mean values of eight patients)*

All of the eight patients tolerated the AlaxoStent without complications and described use as being subjectively comfortable. Day sleepiness was reported, too, to be similarly low as with CPAP therapy. Summarizing, the AlaxoStent demonstrated an unexpected high effectiveness and in many cases absolutely comparable therapeutic efficacy as with CPAP.

Since then numerous propofol sleep video endoscopies (PSE) have visually confirmed the high effectiveness of the AlaxoStent. The published PSE study by Dr. János Juhász (at that time Head of Pulmonology at Mainburg Hospital, Germany) demonstrated a very high and elongated concentric collapse under propofol. The velum including the uvula and the pharynx musculature completely collapsed during sleep. The AlaxoStent secured continuous airway patency for unaffected breathing and thereby eliminated the sleep apnea (see figures in Section 6B and video on the website.)
www.alaxo.com at „AlaxoStent“). The AHI of this patient was reduced from 74/h to 5/h. An AlaxoStent with 30 mm tulip was used. Yet, precise positioning turned out to be important for that the uvula did not collapse underneath the stent and that no concentric collapse occurred above the tulip onto the shaft braid. As a result of this study and other examinations the AlaxoStent with 40 mm tulip has been developed. In a subsequent verification with the same patient with this new AlaxoStent the length of 40 mm has been confirmed by Dr. Juhász to be clearly sufficient. It secured a sufficient therapeutic efficacy also in this challenging case.

The AlaxoStent is being further tested in additional studies (polysomnography, sleep video endoscopy) to obtain broader efficacy data from structured studies, besides therapeutic results from common medical use of the stent.

Literature:
- Scientific poster by Dr. Michael Hartl, MD, et al. at the 80. Annual Conference of the German Society for Oto-Rhino-Laryngology, Head and Neck Surgery e.V. 2009 (May 2009, Rostock, Germany)
- Scientific poster by Dr. János Juhász, MD, at the DGSM Conference 2011 (November 2011, Mannheim, Germany)

9. Further testing of the AlaxoStent

Since early 2012 a growing number of physicians performed numerous PSE studies which almost always led to a very positive result and confirmed the high efficacy of the AlaxoStent therapy. For those patients mostly the soft palate position has been applied. First rare hints towards therapy failures with the AlaxoStent emerge from results of PSE tests in more complicated cases where probably a decreased nasal breathing with low nasal flow may lead to a strong vacuum in the velopharynx. Seemingly this may cause a strong inspiratory collapse of the velopharynx which even the AlaxoStent may not be able to compensate. In such cases amongst other options testing of the parallel application of the AlaxoLito Nasal Stent may be useful in order to normalize nasal breathing.

The second strongest OSA patient who has been successfully treated with the AlaxoStent had an AHI without therapy of 70/h. This was reduced to 15/h with AlaxoStent. The lowest reached AHI under AlaxoStent therapy (with another patient) which is known to Alaxo GmbH is 1.5/h.