Improved Aerosol Therapy

FAVORITE Inhalation

AKITA® JET
FAVORITE Inhalation

Flow And Volume Regulated Inhalation Technology

Innovative Technology

AKITA® JET’s FAVORITE Technology actively regulates inspiration flow as well as inhalation volume. Optimal inhalation patterns can thus be guided and controlled according to therapeutic requirements and the patient’s individual condition. The drug can thus be delivered to the patient’s lungs in an optimal manner and unwanted deposition in the throat is minimized.

FAVORITE offers clear advantages in comparison to conventional inhalation systems – significantly improved utilization of the drug, better reproducibility of lung dosage and targeted deposition of the drug into even the smallest respiratory areas.

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AKITA® JET with FAVORITE

Technology Platform for Optimal Inhalation

Additional tube for air flow
To assist inspiration and volume control.

AKITA® JET Nebulizer Set
Robust, continuous nebulizer with valve system based on Basis PARI LC Sprint®.
High aerosol output of 0.23 ml/min and optimal particle size ø 3.8 μm.

Compressor tube
For generation of drug aerosol.

SMART CARD
Drug-specific cards for recording therapy-related data; contains drug data and information on dosage.

Navigation and Display
• Patient friendly therapy support
• Adjustable settings for patient-specific inhalation time (flexible volume regulation)
• Instructions for therapy
• Feedback on inhalation
• Information on unit progress

FAVORITE
Inhalation technology with optimized inspiration flow and volume control using controlled pressure ventilation and drug aerosol.

Drug Targeting
Electronically controlled inhalation patterns for selective drug deposition into predefined areas of the lung.

Drugs
• Fluticasone, Budesonide, etc.
• Tobramycin, Colistin, etc.
• DNase
• Ipratropium Bromide
• Salbutamol, Formetorol, etc.
• Sodium Chloride solutions
• Other active ingredients

Indications
• Severe Asthma
• Cystic Fibrosis
• Chronic Obstructive Pulmonary Disease (COPD)
• Bronchiectasis
• α1-antitrypsin deficiency
• Pulmonary Hypertension
• Ciliary Dyskinesia
The key to successful inhalation therapy

**Slow Inspiration and High Inhalation Volume**

Inhaling a drug with an optimal particle size does not guarantee sufficient deposition within the lungs. In addition, a patient’s breathing pattern is crucial – the full potency of an inhaled drug can only be reached with slow inspiration flow and a high inhalation volume.

With FAVORITE, the AKITA® JET can electronically regulate both inspiration flow and inhalation volume. This guarantees that these parameters will always be maintained within an optimal range and also ensures a higher drug deposition in the lungs.

Everything that conventional inhalation systems can’t deliver

Reproducibility and Higher Lung Deposition

AKITA® JET guarantees optimal inhalation

- Patients with lung disease generally have variable and sub-optimal breathing patterns, which can negatively affect lung deposition. Conventional inhalation devices are unable to compensate for such complications, as inhalation can occur too quickly (increased inspiration flow) and for an insufficient length of time (reduced inhalation volume).

- FAVORITE resolves this problem – the administration of drug aerosol ensures controlled breathing and optimized inhalation maneuvers. In addition to a higher deposition, FAVORITE maintains low dosage variability and exact reproducibility of the patient’s daily required dose of drugs.

Effective strategies for patients with pulmonary obstructions

Controlled Respiration with Over Pressure

AKITA® JET effectively delivers the drug into all areas of the lung

- AKITA® JET’s FAVORITE concept offers patients with COPD the advantage of flow and volume-controlled respiration using over pressure. The slight increase in pressure is required in order to efficiently deliver the drug to less ventilated areas in the lungs.

- Even inhalation with optimized inspiration and volume can be limited when specific areas of the lung are inaccessible due to obstruction. Special physiotherapeutic procedures, such as pausing during respiration, may help to improve respiration.

FAVORITE Inhalation

Delivering Drugs to the Lower Airways

For certain lung diseases, such as cystic fibrosis or α-1-antitrypsin deficiency, the alveoli must be targeted in order to ensure adequate inhalation therapy. Drug deposition in the alveoli not only depends on a patient’s laryngeal or upper airway morphology, but also on the drug’s particle size as well as inspiration flow and volume.

Scintigraphic depiction of lung deposition in the alveoli of 10 COPD patients after inhalation of radioactive marked, mono-dispersed Fe₃O₄ particles with a flow rate of 200 cm³/s.

AKITA® JET significantly improves drug deposition in the alveoli

AKITA® JET inhalation system fulfills the exact requirements needed in order to deliver the maximum amount of drug aerosol to the alveoli. Flow and volume-controlled inhalation shows a clear superiority in peripheral alveolar deposition compared to conventional nebulizers.

For the very first time in inhaled treatment, AKiTA® JET allows for precise “Drug Targeting”.

- FAVORITE allows continuous control of both aerosolized drugs and air during the inhalation process. Pre-defined variation of the pattern of the drug and air bolus means that the drug deposition can be navigated into either the smaller airways or into the central airways. Depending on the treatment requirements, this location of drug deposition control helps to use drugs more specifically – they can be deposited directly at the place of action, a process called “Drug Targeting”.

- For the very first time, precise pulmonary “Drug Targeting” is now possible for inhalation therapy in combination with AKiTA® JET – depending on the drug and therapeutic goal, drug deposition can easily be adjusted.

- The central airways are targets for bronchodilating drugs – the systemic entry of the drug and subsequent side effects can be avoided by introducing an air bolus into the alveoli beforehand.

- The peripheral airways are targets for the inhalation of substances such as antibiotics or anti-inflammatory drugs. Following inhalation of the aerosolized drug, a small air bolus pushes the aerosol into the obstructed airways.

“Drug Targeting” via continuous control of aerosolized drugs and air.
Exact drug dosage

Safer Inhalation of Antibiotics

AKITA® JET guarantees low variability of lung dosage and reduction of drug deposition in the throat.

- AKITA® JET has several advantages, particularly for drugs with a narrow therapeutic window and high risk of side effects, e.g. antibiotics.
- The inhaled lung dosage can be easily reproduced with low variability.
- Slow regulated inhalation of the aerosolized drug helps significantly reduce throat deposition and avoid potential side effects, such as bronchospasms.

Reducing wastage of expensive drugs

Equivalent Lung Deposition with 50% Less Input Dose

<table>
<thead>
<tr>
<th>Input dose [mg]</th>
<th>Lung deposition [mg]</th>
<th>Serum level [mg x 10/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>250</td>
<td>200</td>
</tr>
<tr>
<td>150</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

• With FAVORITE, nebulization occurs only during inspiration – when combined with AKITA® JET and controlled breathing techniques, FAVORITE inhalation allows for expensive drugs to be used fully and efficiently.

• In comparison to conventional nebulizers, AKITA® JET can provide equivalent lung dosing with a significantly reduced input dose, allowing for a 50% reduction in drug investment depending on the drug. Using AKITA® JET for the inhalation of high-dose Tobramycin could save patients more than €1,000 per month (based on average market prices in Europe).

AKITA® JET – an investment that quickly pays off by saving expensive drugs

Lung deposition and serum level in 12 healthy volunteers after inhalation of Tobramycin. Cross-over inhalation test.

Increasing therapeutic quality

Effective Inhalation and Shorter Treatment Time

AKITA® JET provides high quality therapy within a short treatment period

Mesh nebulizers create large amounts of drug aerosol, which allows for a shorter treatment period. However, the quality of this kind of inhalation is questionable. When continuous aerosol nebulization is combined with sub-optimal and variable inspiration, a large amount of the drug is often wasted and the inhaled drug deposition can vary widely.

The AKITA® JET inhalation system uses a reliable and robust jet nebulizer technology for aerosol generation. In comparison with a jet nebulizer using a normal compressor, a jet nebulizer combined with AKITA® JET significantly decreases inhalation time. Each inspiration with AKITA® JET is highly efficient with regard to the amount of drug deposited in the lungs per breath, meaning that fewer breaths are needed in order to reach the required dosage. AKITA® JET also decreases the inhaled treatment time typically required for high volume drug formulations to just under 10 minutes.


I nhal at i on t i me f or Tobramyci n 3 00 mg /4 ml, AKITA® JET vs. mesh nebulizer and conventional jet nebulizer.
New treatment options
Greater Lung Dosing with FAVORITE

Compared to conventional inhalation systems, AKITA® JET allows for a significantly higher drug deposition in the lungs even with average dosing.

<table>
<thead>
<tr>
<th>Particle size [MMAD]</th>
<th>Dose at the mouthpiece [µg]</th>
<th>Lung dose [µg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPI 4.10 µm</td>
<td>210</td>
<td>55</td>
</tr>
<tr>
<td>PARI Turbo Boy N 4.26 µm</td>
<td>367</td>
<td>142</td>
</tr>
<tr>
<td>AKITA® JET 3.76 µm</td>
<td>655</td>
<td>497</td>
</tr>
</tbody>
</table>

In vitro study with Fluticasone: Drug concentration at the mouthpiece and lung deposition measured using different inhalation systems.

- With a normal 2 mg/2ml dose of Fluticasone, AKITA® JET can achieve a lung dose four times higher than normal as compared to conventional nebulizers and nine times more than with a Dry Powder Inhaler (DPI). AKITA® JET deposits 75% of the dose measured at the mouthpiece into the lungs, whereas conventional nebulizers only reach a deposition rate of 39% and DPI’s only 26%.

- AKITA® JET’s outstanding efficacy ensures that a higher drug dose can be deposited into the lungs. A drug deposition of 75% not only shows efficient use of the drug, but it also shows that only a minimal amount is deposited in the throat – thus, a higher lung dose is possible without raising the risk of possible negative side effects.

Müllinger et al. 2008; Drug Output of Inhalers is not a Predictor of Lung Dose. Abstracts of the RDD Conference, Respiratory Drug Delivery 2008; Arizona, USA.
Therapeutic outlook for severe asthma

High Dose Inhalation of Steroids

Possible benefit from high dose inhalation with AKITA® JET – first clinical data

- 112 severe asthma patients with a need for permanent treatment with oral corticosteroids received a high dose of inhaled Fluticasone as an add-on therapy using AKITA® JET. The retrospective data analysis showed significant improvements after three weeks. Lung function improved on average by 17%, the need for oral corticosteroids could be reduced by 30% and NO-measurements showed that pulmonary inflammation was reduced by 40%.

- Because of this promising data, ACTIVAERO has initiated a clinical program to validate this therapeutic approach. A first randomized, double blind, placebo-controlled multi-centre study is underway.

- The first clinical data with Fluticasone give an outlook how the high dose inhalation with AKITA JET could be used to develop new treatment regimes in the future. ACTIVAERO’S intends to achieve an improved clinical response and a reduction in systemic treatment and prevention of related side effects. In Asthma, for example, the long-term use of systemic corticosteroids carries safety risks such as osteoporosis and diabetes.

Add-on Therapy with AKITA® JET: 2 mg/2 ml Fluticasone per day; 112 patients with severe asthma treated with oral Corticosteroids, no placebo group has been tested.

Two fundamental options for therapy

Better Equivalent or Higher Maximum Dosing

Equivalent dosing with AKITA® JET:
Shorter inhalation time and reduced drug consumption

<table>
<thead>
<tr>
<th>PARI boy N; LC Plus</th>
<th>AKITA®; LC Star</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>300 mg</td>
</tr>
<tr>
<td>Nebulized dose</td>
<td>240 mg</td>
</tr>
<tr>
<td>Therapy time</td>
<td>20 min</td>
</tr>
<tr>
<td>Serum level after 1 hour</td>
<td>1.2 ± 0.78 mg/L</td>
</tr>
</tbody>
</table>

- With AKITA® JET, equivalent drug doses (like those shown in scientific study results with conventional nebulizers) can be achieved, but with additional advantages:
  - Better reproducibility of dosing
  - More precise drug targeting
  - Less drug consumption
  - Less throat deposition
  - Better drug deposition in obstructive patients
  - Reproducible therapy time

Maximum dosing with AKITA® JET:
An ongoing clinical program is checking possible benefits for the treatment of Asthma

<table>
<thead>
<tr>
<th>After 3 Weeks add-on inhalation</th>
<th>Maximum dose of Fluticasone with AKITA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of FEV1</td>
<td>+ 17.2%</td>
</tr>
<tr>
<td>Reduction of systemic steroid dose</td>
<td>− 33.2%</td>
</tr>
<tr>
<td>Additional side effects</td>
<td>None</td>
</tr>
</tbody>
</table>

- Based on different therapeutic indications, AKITA® JET also offers the option to maximize drug dosage in the lungs – possible advantages for new treatment regimes in the future are:
  - Higher local effect
  - Reduction or avoidance of a systemic therapy


2.) Jung et al. 2008; Treatment of Patients with uncontrolled Asthma using high dose inhaled Corticosteroids administered by controlled Inhalation – A retrospective Analysis. ERJ Volume 34, Supplement 53 Sept 2009.
The SMART CARD
Specific Therapy Control

The SMART CARD is an electronic chip card that provides and controls all relevant therapy parameters, such as the drug and dosage-specific inhalation information for AKITA® JET. Furthermore, all treatment data can be stored on the SMART CARD. This allows physicians, physiotherapists and patients to optimize the therapy using a computer-based compliance analysis.

Drug-specific
One SMART CARD per drug and dosage e.g. Colistin antibiotic – starting dose 1 Mio. IE Colistin in 3 ml solvent.

Adapted to the patient
The AKITA® Display allows the patient to quickly and effectively adapt inhalation time per breath to his or her own inhalation capabilities – the chosen inhalation time determines the inhalation volume per breath.

<table>
<thead>
<tr>
<th>Inhalation time per breath</th>
<th>Total number of breaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 sec (0.3 l)</td>
<td>84</td>
</tr>
<tr>
<td>2.0 sec (0.4 l)</td>
<td>56</td>
</tr>
<tr>
<td>2.5 sec (0.5 l)</td>
<td>46</td>
</tr>
<tr>
<td>3.0 sec (0.6 l)</td>
<td>36</td>
</tr>
<tr>
<td>3.5 sec (0.7 l)</td>
<td>33</td>
</tr>
<tr>
<td>4.0 sec (0.8 l)</td>
<td>28</td>
</tr>
<tr>
<td>5.0 sec (1.0 l)</td>
<td>21</td>
</tr>
<tr>
<td>6.0 sec (1.2 l)</td>
<td>17</td>
</tr>
<tr>
<td>7.0 sec (1.4 l)</td>
<td>14</td>
</tr>
<tr>
<td>8.0 sec (1.6 l)</td>
<td>12</td>
</tr>
</tbody>
</table>

There is one SMART CARD for each drug and dosage and this determines the exact drug dose and deposition area in the lung. A patient can control the SMART CARD via the AKITA® JET display. The patient can select their breathing capacity by selecting their personal inspiration time or volume – a measurement of lung function can provide a recommendation for this setting.

Based on this patient-specific information, the AKITA® JET calculates the number of breaths necessary to inhale the required lung dose. The treatment automatically finishes when the complete lung dose has been inhaled – in this way, under and over dosing can be prevented.
Analyzing and optimizing patient compliance

Therapeutic Success is Measurable

Treatment record and evaluation using the SMART CARD

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Number of breaths</th>
<th>Therapy time [min]</th>
<th>Target breaths</th>
<th>Inhaled dose [%]</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-04-09</td>
<td>08:32</td>
<td>21</td>
<td>3.45</td>
<td>21</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>01-04-09</td>
<td>08:34</td>
<td>21</td>
<td>3.55</td>
<td>21</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>02-04-09</td>
<td>08:16</td>
<td>21</td>
<td>4.01</td>
<td>21</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>02-04-09</td>
<td>18:34</td>
<td>21</td>
<td>4.25</td>
<td>28</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>02-04-09</td>
<td>08:01</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0%</td>
<td>MSS</td>
</tr>
<tr>
<td>03-04-09</td>
<td>20:10</td>
<td>21</td>
<td>3.39</td>
<td>21</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>03-04-09</td>
<td>08:32</td>
<td>--</td>
<td>--</td>
<td>28</td>
<td>0%</td>
<td>MSS</td>
</tr>
<tr>
<td>04-04-09</td>
<td>18:34</td>
<td>21</td>
<td>3.55</td>
<td>21</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>05-04-09</td>
<td>08:16</td>
<td>21</td>
<td>4.01</td>
<td>21</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>05-04-09</td>
<td>19:02</td>
<td>28</td>
<td>4.25</td>
<td>28</td>
<td>100%</td>
<td>HIT</td>
</tr>
<tr>
<td>05-04-09</td>
<td>09:01</td>
<td>--</td>
<td>--</td>
<td>21</td>
<td>0%</td>
<td>MSS</td>
</tr>
<tr>
<td>05-04-09</td>
<td>20:10</td>
<td>21</td>
<td>3.39</td>
<td>21</td>
<td>100%</td>
<td>HIT</td>
</tr>
</tbody>
</table>

... ... ...

22-04-09 | 09:01      | --                | --                 | 21             | 0%               | MSS    |
| 22-04-09 | 20:10      | 21                | 3.48               | 21             | 100%             | HIT    |
| 23-04-09 | 08:32      | --                | --                 | 28             | 0%               | MSS    |
| 23-04-09 | 18:34      | --                | --                 | 28             | 0%               | MSS    |
| 24-04-09 | 08:32      | 21                | 3.40               | 21             | 100%             | HIT    |
| 24-04-09 | 18:34      | 21                | 3.32               | 21             | 100%             | HIT    |
| 25-04-09 | 08:16      | --                | --                 | 21             | 0%               | MSS    |
| 25-04-09 | 19:02      | 28                | 4.33               | 28             | 100%             | HIT    |
| 26-04-09 | 09:01      | --                | --                 | 21             | 0%               | MSS    |
| 26-04-09 | 20:10      | 21                | 3.29               | 21             | 100%             | HIT    |
| 27-04-09 | 08:32      | 21                | 3.46               | 21             | 100%             | HIT    |
| 27-04-09 | 18:34      | 21                | 3.56               | 21             | 100%             | HIT    |
| 28-04-09 | 08:16      | 12                | 2.01               | 28             | 50%              | incomplete |
| 28-04-09 | 19:02      | 14                | 2.15               | 28             | 50%              | incomplete |

Example of therapeutic data recorded on the SMART CARD for the inhalation of Colistin. 1 Mio. IE over 28 days.

THERAPEUTIC DATA

- Treatment period: 28 days
- Inhalation time per breath: 4.0 – 5.0 sec
- Inhalation volume: 0.8 – 1.0 l
- Necessary treatments: 56
- Completed treatments: 46
- Skipped treatments: 8
- Partial treatments: 2
- Average treatment time: 4.09 min

COMPLIANCE ANALYSIS [%]

- Number of breaths per treatment
- Treatment time
- Timing of treatment, e.g. morning vs. evening
- Inhaled drug dosage, e.g. over all dose and seven-day dose

The SMART CARD saves all therapeutic data: Data can be read and analyzed using a PC. This data is not only interesting in a clinical study setting, but also during outpatient procedures. This enables both doctor and patient to easily analyze and optimize compliance.

Compliance analysis via SMART CARD provides information on:

- Number of breaths per treatment
- Treatment time
- Timing of treatment, e.g. morning vs. evening
- Inhaled drug dosage, e.g. over all dose and seven-day dose
## Technical details

### Overview of AKITA® JET

<table>
<thead>
<tr>
<th><strong>AKITA® JET Control unit</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation flow</td>
<td>12 l/min</td>
</tr>
<tr>
<td>Weight</td>
<td>2.85 kg</td>
</tr>
<tr>
<td>Size (L x H x B)</td>
<td>206 x 180 x 130 mm (including nebulizer)</td>
</tr>
<tr>
<td>Electric protection category</td>
<td>II Typ B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>AKITA® JET Power supply</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>FRIWO</td>
</tr>
<tr>
<td>Model</td>
<td>DT50 Medical</td>
</tr>
<tr>
<td>Type</td>
<td>FW7405M/24</td>
</tr>
<tr>
<td>Input voltage</td>
<td>100–240 V / 50–60 Hz / 1.1 A</td>
</tr>
<tr>
<td>Output voltage</td>
<td>24 VDC 2.2 A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>AKITA® JET Nebulizer Set</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>PARI</td>
</tr>
<tr>
<td>Model</td>
<td>LC Sprint®</td>
</tr>
<tr>
<td>min. Input volume</td>
<td>2 ml</td>
</tr>
<tr>
<td>max. Input volume</td>
<td>8 ml</td>
</tr>
<tr>
<td>Flow rate</td>
<td>12 l/min</td>
</tr>
<tr>
<td>Aerosol release</td>
<td>0.23 ml/min</td>
</tr>
<tr>
<td>MMAD – Mass Median Aerodynamic Diameter</td>
<td>3.8 μm (sodium fluoride solution 1.0 %)</td>
</tr>
</tbody>
</table>

### Additional Information

- Germany: HMZ 14.24.01.3002
- Europe: in accordance with 93/43/EWG
- USA: cleared in the USA (K090730)
- Commercial launch: 2008
- Manufactured in: Germany
- Producer: ACTIVAERO
- Distribution, technical service, reimbursement: National medical technology partner
Notes

Notes and Personal Information
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