PORCINE BRAIN: FACTS OR FICTION

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Pharmacological Profile

Effects of the Peptides

1. Neurolrophic Stimulation: secures the survival and differentiation and protects nerve cells from insults
2. Neuromodulation: improves behaviors, memory learning, changes of neuronal and synaptic plasticities
3. Metabolic Regulation: protects nerve cells of the brain from lactate acidosis and improves oxygen utilization inside the nerve cells

Mechanisms of Action

1. Its action assumed to be similar to naturally occurring neurotrophic factors (NGF) which are a group of proteins with characteristic effects:
   - Neuronal differentiation (sprouting of axons and dendrites)
   - Maintenance of the functional integrity of the nerve cells
   - Protection the nerve cells from lesions
   - R. Levi-Montalcini discovered neurotrophic factors or NGF in 1950s

Neurotrophic Stimulation

Cerebrolysin improves the survival of brainstem of chick embryo (Albrecht et al., 1992)

Cerebrolysin® ...

- Peptide preparation produced by the biotechnological standardized enzymatic breakdown of purified porcine brain proteins
- Consists of ~ 15% peptides with a MW not exceeding 10kD and 85% AA based on total nitrogen
- The solution, ready for injection or infusion, is free of proteins, lipid and antigenic properties
- 1 ml of Cerebrolysin® contains 215.2 mg of porcine brain-derived peptide preparation in aqueous solution
Neurotrophic Stimulation
Nerve cell culture without Cerebrolysin

Neurotrophic Stimulation
Nerve cell culture with Cerebrolysin

Neurotrophic Stimulation
Cerebrolysin on brain protein synthesis of old rats

Neurotrophic Stimulation
Cerebrolysin decreases free radicals in ischemia

Neurotrophic Stimulation
Cerebrolysin facilitates regeneration of cholinergic neurons after septohippocampal transection

Neurotrophic Stimulation
Cerebrolysin delays cell death in an ischemia/reperfusion model
Neuromodulation
Cerebrolysin increases synaptic density, plasticity and performance

I Cerebrolysin increases the synaptic density in the hippocampus, dentate gyrus and the entorhinal cortex of 24-month-old rats. (Reinberg I, et al., Histochem J 1999:31:395-403)


Neuromodulation
Cerebrolysin decreases beta-amyloid deposition


Metabolic regulation

Metabolic regulation
Cerebrolysin facilitates oxygen utilization in rat brain homogenates

Metabolic regulation
Cerebrolysin prevents lactate acidosis in rat brain
Cerebrolysin® ...

- Is in clinical use since many years and currently available in 25 countries
  - Germany
  - Austria
  - Portugal
  - ...
- Has IND status in USA and Canada
  - US FDA approval March 1998
  - Canadian HPB approval August 1995
  - Is available for clinical use in Canada through HPB’s Emergency Drug Release program

Clinical Trial Data

- More than 70 clinical studies published to date, with over 4,200 patients enrolled
  - Dementia
  - Stroke
  - Brain Injuries
- Recent studies in Alzheimer’s disease
  - German GCP Study (Ruether, 1994)
  - Austrian Phase IV Study (Rainer, 1997)
  - Canadian GCP Study (Panisset & Gauthier, 1999)
  - German/Austrian GCP Study (Ruether, 1999)

Objective

- Assessment of safety and efficacy of Cerebrolysin®
- Investigation of repeated treatment courses
- Investigation of long-term effects after drug withdrawal

Efficacy Measures

- Primary
  - Global function
  - Cognitive Performance
  - CGI-C
  - ADAS-COG
- Secondary
  - Behaviour
  - Activities of Daily Living
  - Depressive Symptoms
  - ADAS-NONCOG
  - NAB
  - MADR-S

Safety Measures

- Adverse Events
- Lab Parameters
  - Vital Signs

Patient Population

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Men or Women</td>
<td>CT or MRI Incompatible with Diagnosis of AD</td>
</tr>
<tr>
<td>Age 50–85 Years</td>
<td>Vascular Dementia</td>
</tr>
<tr>
<td>NINCDS-ADRSA</td>
<td>Other Neurological Diseases</td>
</tr>
<tr>
<td>ICD-10</td>
<td>Severe Concomitant Illnesses</td>
</tr>
<tr>
<td>MMSE 14–24</td>
<td></td>
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<tr>
<td>CGI – Severity of Disease &gt; 2</td>
<td></td>
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</tbody>
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Dosage & Treatment

- Dosage
  - Group A: 30 ml Cerebrolysin® + 70 ml Saline Solution
  - Group B: 100 ml Saline Solution
- Total of 40 IV Infusions, Once Daily

- Treatment Schedule
  - Treatment 1: 5 Days/Week for 4 Consecutive Weeks
  - 2-Month Treatment-Free Interval
  - Treatment 2: 5 Days/Week for 4 Consecutive Weeks
Efficacy Analysis

- Primary Endpoint: Month 4 Visit
- Primary Parameters: CGI-C, ADAS-COG
- Primary Population: ITT
- Scoring Option: LOCF

... Cerebrolysin® produces a statistically significant improvement over Placebo in both primary efficacy parameters ...

Results

- Primary Outcome Measures
- Secondary Outcome Measures
- Safety Data

Sandoz Clinical Assessment-Geriatrics (SCAG)

Clinical Global Impression (GCI)

CGI-C - Score Distribution

CGI-C - Responder
Alzheimer's Disease Assessment Scale-Cognitive Function (ADAS-COG)

Responder: ADAS & CGI-C

Vascular Dementia - (Arnold-Hohlmann test)

Open Clinical Trial in Dementia - CGI
**Secondary Measures**

- **Behaviour**
- **Activities of Daily Living**
- **Depressive Symptoms**
- **Cognition/Concentration**
- **ITT-LOCF Analysis**

- ADAS-NONCOG
- NAB
- MADR-S
- SKT
- Cerebrolysin® n=74
- Placebo n=70

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**ADAS-NONCOG – Behavioural Disturbances**

Mean Change from Baseline

- ADAS-NONCOG Score
- Cerebrolysin®
- Placebo

- Time (Months)

- P=0.002
- P=0.003
- P=0.020

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**Activities of Daily Living (ADL)**

Mean Change from Baseline

- ADL
- Cerebrolysin
- Placebo

- P=0.071

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**ADL – Responder**

- Month 1
- Month 4
- Month 7

- Cerebrolysin
- Placebo

- P=0.014

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**MADRS – Depressive Symptoms**

Mean Change from Baseline

- MADRS
- Cerebrolysin
- Placebo

- P=0.020

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**Open Clinical Trial in Stroke - ADL**

- Improved
- Unchanged
- Worse

- % of Patients

- 0 20 40 60 80 100
Safety Analysis

- Adverse Events
- Lab Parameters
- Vital Signs
- Safety Population

Cerebrolysin® n=76
Placebo n=71

Lab & Vital Signs

- No significant change in any of the lab parameters in both groups
- No change in vital signs
  - pre- and post infusion
  - as well as over time

Adverse Events

- No differences in AEs between Cerebrolysin® and Placebo groups

Summary

- Cerebrolysin® leads to statistically significant and clinically relevant improvement in both cognition and global function in patients with AD
  - This is supported by findings in the secondary parameters, where significant improvement was evident in behaviour, depressive symptoms and activities of daily living
  - Cerebrolysin® is safe and well tolerated

Conclusions

- Patients on Cerebrolysin® had significantly greater improvement than Placebo-treated patients after only one month of treatment

  - Acute symptomatic improvement
  - Fast onset of action

Conclusions

- Second Cerebrolysin® treatment after a treatment-free interval reinforces therapeutic improvement
  - Patient's response to the second treatment is equal or greater than to the initial treatment

  - Therapeutic concept: Long-term Cerebrolysin® treatment with therapy-free intervals