Dexolve™
the USP compliant SBECDD
of Cyclolab Ltd
Cyclolab Ltd is the producer of the first generic USP-conform Betadex Sulfobutyl Ether Sodium (SBECD = Dexolve™) for Improved Pharmaceutical Formulations.
Cyclolab Ltd is the producer of the first generic USP-conform Betadex Sulfobutyl Ether Sodium (SBECSD = Dexolve™)

Drug master file of the excipient Sulfobutyl-ether-β-cyclodextrin sodium salt (SBECSD)

Document No.: DMF-SBECSD-v02
Why use Dexolve? Possibilities…

- Significant solubility enhancement (10 to 100,000 fold)
- Improvement of chemical stability
- Increased bioavailability, facilitated delivery
- Reduced aggregation
- Moderate irritation or reduced side-effects
- Maximized patient safety, complete renal elimination
- Enables formulation of water-insoluble APIs in all dosage forms
- Lower API doses can be achieved
There are 10 APIs on the market and at least 60 further in development in formulations containing SBECID including:

- Voriconazole
- Carfilzomib
- Amiodarone
- Ziprasidone
- Maropitant (veterinary use)
- Aripiprazole
- Posaconazole
- Carbamazepine
- Melphalan
- Delafloxacin

- Mebendazol
- Topiramate
- Omeprazole
- Clopidogrel
- Docetaxel
- Meloxicam
- Allopregnanolone

Several other nitrogen containing API bases are in various clinical phases
Main regulatory/QA/sales aspects:

- **Maintained DMF** for SBEC in US and Canada since 2008

- Prepared via a self-developed **proprietary, patented technology** with a process **independent from any existing patents (expires in 2031)**

- **36-month stability** data

- Successful production of over 100 subsequent USP compliant batches – no OOS result
Dexolve™
for Improved Pharmaceutical Formulations

Main regulatory/QA/sales aspects:

- Dedicated production facility with a capacity of over 12000 kg/year (extendable to 20-30,000 kgs/yr without investment)

- 120 kg batch size

- Quality system compliant to ISO 9001 and GMP requirements (regularly audited)

No down payment, No milestone payment, No royalty payment
Main regulatory/QA/sales aspects:

- Over 30 APIs in development using Dexolve

- Over 60 partners in commercial and development phases using Dexolve

- Research grade material available at reduced price for non-clinical development

- Flexible business model to handle partners’ requests and provide technical support on development
Dexolve™
for Improved Pharmaceutical Formulations

Available reference materials:

- Betadex
- 4-Hydroxybutane-1-sulfonyc Acid
- Bis(4-sulfobutyl) Ether Disodium
- 1,4-Butane Sultone
- Betadex Sulfobutyl Ether Sodium
# Dexolve™

**for Improved Pharmaceutical Formulations**

## RELEASE SPECIFICATION (USA/CA)

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearanceprivate</td>
<td>Visual (125x100)</td>
<td>White or off-white powder</td>
</tr>
<tr>
<td>Identification A</td>
<td>HPLC; USP &lt;919&gt;, EP 2.2.29</td>
<td>No major peaks (cf. USP reference)</td>
</tr>
<tr>
<td>Identification B (Assay method)</td>
<td>HPLC; USP &lt;919&gt;, EP 2.2.29</td>
<td>No major peaks (cf. USP reference)</td>
</tr>
<tr>
<td>Identification C</td>
<td>CE; USP &lt;1053&gt;, EP 2.2.47</td>
<td>Average degree of substitution: 6.2 - 6.9</td>
</tr>
<tr>
<td>Identification D</td>
<td>Sodium ID; USP &lt;919&gt;, EP 2.3.1</td>
<td>Positive test</td>
</tr>
<tr>
<td>Assay #</td>
<td>HPLC; USP &lt;919&gt;, EP 2.2.29</td>
<td>95.0-105.0% on the anhydrous basis</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>ICP-MS, USP &lt;232.233&gt;</td>
<td>Sodium NMT 0.2 mg/g; Calcium NMT 0.2 mg/g; Lead: NMT 0.5 mg/g; Arsenic NMT 1.5 mg/g; Mercury NMT 0.3 mg/g; Chromium NMT 110 mg/g; Nickel NMT 2 mg/g; Molybdenum NMT 150 mg/g; Vanadium NMT 1 mg/g</td>
</tr>
<tr>
<td>Limit of related substances #</td>
<td>HPLC USP &lt;919&gt;, EP 2.2.29</td>
<td>NMT 0.1% (Published 0.3%)</td>
</tr>
<tr>
<td>Beta Cyclodextrin (Betadex)</td>
<td>HPLC USP &lt;919&gt;, EP 2.2.29</td>
<td>NMT 0.1% (Published 0.3%)</td>
</tr>
<tr>
<td>Limit of 1,4-Butane Sultone</td>
<td>GC; USP &lt;919&gt;, EP 2.2.29</td>
<td>NMT 0.5 ppm</td>
</tr>
<tr>
<td>Limit of Sodium Chloride</td>
<td>Limit test; USP &lt;919&gt;</td>
<td>NMT 0.2% (Published 0.3%)</td>
</tr>
<tr>
<td>Limit of 4-Hydroxybutane-1-sulfonic Acid</td>
<td>CE; USP &lt;1053&gt;, EP 2.2.47</td>
<td>NMT 0.09%</td>
</tr>
<tr>
<td>Limit of Bis(4-sulfobutyl) Ether Disodium</td>
<td>CE; USP &lt;1053&gt;, EP 2.2.47</td>
<td>NMT 0.05%</td>
</tr>
<tr>
<td>Bacterial Endotoxin Test #</td>
<td>EP-USP harmonized method</td>
<td>≤ 24 IU/g</td>
</tr>
<tr>
<td>Microbial Enumeration Tests #</td>
<td>EP-USP harmonized method</td>
<td>TAC ≤ 100 cfu/g; TVMC ≤ 50 cfu/g</td>
</tr>
<tr>
<td>Test for Specified Microorganism</td>
<td>EP-USP harmonized method</td>
<td>Absence of Escherichia Coli / St. g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate content</td>
<td>UV-Vis Spectrophotometry (USP &lt;851&gt;); EP 2.2.25</td>
<td>525-700 μg/g</td>
</tr>
<tr>
<td>Clarity of solution (30%, w/v) #</td>
<td>Visual; see details in the USP Monograph, EP 2.2.1</td>
<td>The solution is clear and essentially free from particles of foreign matter</td>
</tr>
<tr>
<td>Average Degree of Substitution [DS]</td>
<td>CE; USP &lt;1053&gt;, EP 2.2.47</td>
<td>6.2 - 6.9</td>
</tr>
</tbody>
</table>

**Packaging and Storage:** Preserve in well-closed containers, store at room temperature. Protect from moisture. Labelling: indicate its use in the manufacture of injectable dosage forms.

**Completely USP compliant!**
Company contacts – ASK FOR A FREE SAMPLE:
CycloLab Cyclodextrin Research & Development Laboratory Ltd.
Budapest, P.O. Box 435, H-1525 Hungary
Location: Illatos út 7., Budapest, H-1097- Hungary
TEL: (+36) 1-347-60-60 or -70; FAX: (+36) 1-347-60-68
E-mail: dexolve@cyclolab.hu; Homepage: http://www.cyclolab.hu

Contact person: Tamas Sohajda, PhD
R&D Director
sohajda@cyclolab.hu  Tel: (+36) 1-347-60-72
User’s guide for Dexolve-7

A simple 3-step manual for successful dissolution of your drug substance
Weigh in the following Dexolve-7 amounts into 20 ml vials and prepare solutions with the given volume of distilled water:

<table>
<thead>
<tr>
<th>Dexolve-7*</th>
<th>Distilled water</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 g</td>
<td>7.0 mL</td>
</tr>
<tr>
<td>2.0 g</td>
<td>8.0 mL</td>
</tr>
<tr>
<td>1.0 g</td>
<td>9.0 mL</td>
</tr>
<tr>
<td>0.5 g</td>
<td>9.5 mL</td>
</tr>
</tbody>
</table>

*for accurate results take the water content of Dexolve-7 into consideration

Use stirrer bar and magnetic stirrer.
- After the complete dissolution of Dexolve-7, add ~50 mg or appropriate volume of your drug (candidate) to each vial. Should you be short of material, take smaller volume of the Dexolve-7 solutions and dispense reduced amount of your substance, accordingly.

- Stir the resulting suspensions for 24 hours at room temperature. If your substance is sensitive, then cool your samples and protect them from light in the meantime.

- Observe the vials. If your substance completely dissolves upon stirring, dispense additional amount of your substance. Always ensure excess of material to be dissolved.
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for Improved Pharmaceutical Formulations

- When finished, filter the suspensions through PVDF syringe filters.

- Analyze the filtrate for your drug content.

- Establish relationship between the concentrations of Dexolve-7 and the solubilized amounts of drug substance. Compare the data with the pure aqueous solubility of your substance.

*In case you need technical help to facilitate the dissolution or to improve the solubilizing potency further, contact us!*