



The Cyclodextrin Company

Getting the best out of Cyclodextrins

CYCLOLAB Ltd.

Solubilization of Panobinostat with cyclodextrins for anticancer therapies



Multiple myeloma

- Cancer of plasma B cells
- The are white blood cells originating from the bone marrow
- The cancerous plasma cells produce abnormal antibodies instead of normal ones
- Causes bone pain, anemia, kidney problems, infection or neurological symptoms



Ref: Wikipedia; <u>https://www.hematologyadvisor.com/</u>; Picture credit: ©2019 Jackie Heda, Biomedical & Scientific Visuals



- Tumor located in the middle of brain stem
- Glioma is a group term for a tumor that arise from glia
- DIPG is brainstem glioma
- 5-year survival rate: <1%
- Treatments: neurosurgery not possible, radiotherapy, chemotherapy
- Difficulty in treatment, overcoming the blood-brainbarrier (BBB)





- A group of about 50 **rare** genetically inherited metabolic disorders
- Disrupts the metabolism of lipids, glycoproteins or polysaccharides
- Usually connected to the misbehavior of one specific enzyme
- Few examples: Niemann Pick disease type C, Fabry disease, Hunter syndrome, Gaucher disease



Ref: Wikipedia; Kontinnen et al (2019) Biometals in Neurogenerative Diseases



How panobinostat works

- Antineoplastic agent, Histone deacetylase (HDAC) inhibitor
- DACs are overexpressed in myeloma patients
- Inducing apoptosis of malignant cells: cell death
- Similar action in the case of lysosomal storage diseases



Ref + Picture credit ©2015: Laubach et al (2015) Panobinostat for the treatment of Multiple Myeloma (Clinical Cancer Research)



Panobinostat

- Trade name: Farydak (Novartis)
- Antineoplastic agent, Histone deacetylase inhibitor, inducing apoptosis of malignant cells
- Indication: for cancer treatment (multiple myeloma)
- Fast absorption from the gut, but **low bioavailability (21%)** due to first-pass effect
- 315 major drug interactions, 209 moderate drug interactions
- Clinical stage indications:
 - Lymphomas
 - Graft versus Host Disease
 - HIV/AIDS
 - Glioma
 - Lysosomal Storage Disease (Niemann Pick Type C)





Market forecast

Panobinostat forecasted sales from Farydak



Source: Globaldata, data based on predicted Farydak sales







- Water Solubility: 0.002 mg/mL (estimated)
- logP: 2-3
- Patients receive **oral** Panobinostat in **capsules** with 10-15-20 mg API
- No injections were developed due to the low aqueous solubility

FARYDAK 20 mg

6 Kapsol

NOVARTIS



Midatech Pharma Ltd., (2016) Coulter et al.; GB20160005406
 Cyclodextrin-panobinostat adduct
 WO2017167837A1 Patent in investigational phase
 EP3347055 Decision was made to grant a European patent (2019)

Uses Hydroxypropyl beta-cyclodextrin (HPBCD)

Brain tumor

Midatech (Cardiff): An R&D company focused on delivering innovative oncology and rare disease products to patients

2019 FDA orphan designation for solubilized form of panobinostat (MTX110) in childhood brain cancer: Diffuse Intrinsic Pontine Glioma (DIPG)

Phase I and Phase II

Midatech Pharma announces confirmation of a €2.6 million EU Grant for further clinical development of MTX110 for the treatment of Diffuse Intrinsic Pontine Glioma, a rare and fatal form of childhood brain cancer



 RaNeDis Pharmaceuticals, LLC (2016) Claypool; US201662360012 Compositions and methods of treating and/or preventing lysosomal storage diseases and other monogenetic metabolic diseases. WO2018009531 Patent in investigational phase Withdrawn in EPO countries Using HPBCD and SBECD

Mainly for vorinostat, Panobinostat is mentioned Indication: Niemann Pick C and other lysosomal storage diseases

RaNeDis Pharmaceuticals, LLC (2017) Claypool; US201762516251
 Compositions and methods of treating and/or preventing cancer
 WO2018226939A1 Patent in investigational phase
 Using HPBCD and SBECD
 Mainly for vorinostat, Panobinostat is mentioned
 Indication: brain tumor

• Rare and Neglected Diseases

• RND-001 formulation has resulted in dramatic improvements of function and survival in a mouse transgenic model of Niemann-Pick Type C disease. Licensed from the Univ. Of Notre Dame.

CYCLIGLAB Clinical studies of Panobinostat

- Midatech Pharma: MTX110 panobinostat in solution
 - Brain Cancer (Phase I/II)
- Novartis: Farydak tablets
 - Multiple Myeloma (Approved)
 - AIDS (Phase I/II)
 - Brain Cancer (Phase I/II)
 - Breast Cancer (Discovery)
 - Graft Versus Host Disease (Phase I/II)
 - Huntingtons Disease (Pre-clinical)
 - Kidney Cancer (Phase I/II)
 - Lung Cancer (Phase I)
 - Pancreatic Cancer (Discovery)
 - Prostate Cancer (Phase II)
 - Sickle Cell Anemia (Phase I)
 - Soft Tissue Sarcoma (Phase I)
 - Solid Tumors (Phase I)
 - Thyroid Cancer (Phase II)



Formulation of Panobinostat with cyclodextrin

• Midatech

- 40 µM Panobinostat with HPBCD, which is 0.11 mg/ml
 Panobinostat in solution
- Formulation is a lyophilized powder
- In one clinical trial a dose of 0.5 ml of 300 µM (0.85 mg/ml) MTX-001 solution is used
- In another clinical trial 30-60-90 µM MTX-001 is used (Panobinostat), the highest concentration is 0.26 mg/ml
- Ranedis
 - examples only with vorinostat
 - RND001 is not Panobinostat
 - They use HPBCD and SBECD for solubilization (up to 5 mg/ml)



Cyclolab's procedure

10 mg/ml Panobinostat is achievable in solution

The technology improvements invented at Cyclolab enable successful circumvention of all existing patents in this field.



Company contacts

CycloLab Cyclodextrin Research & Development Laboratory

Ltd. Budapest, P.O. Box 435, H-1525 Hungary

Location: Illatos út 7., Budapest, H-1097 Hungary

TEL: (+36) 1-347-60-70

FAX: (+36) 1-347-60-71

E-mail: info@cyclolab.hu

Website: <u>http://cyclolab.hu/</u>

Contact person:

Tamas Sohajda

R&D Director

info@cyclolab.hu

Tel: (+36) 1-347-60-72