

# ENSPYR

## Non-confidential Info Pack

# Opportunity

- ENSPYR:
  - Vast commercial potential in depression market
  - Superior safety profile
  - Addressing three most important unmet medical needs:
    - Improved efficacy
    - Faster onset of action
    - Better side effect profile
  - Extensive period of market exclusivity
    - Long patent life
    - Relatively short time-to-market
  - Low technical and developmental risk

# Depression Market

- Huge market
  - Continuous growth until 2010 when it peaks at \$ 15 bln
  - From 2011 to 2016 market will decline due to generic erosion after which further growth is anticipated
- Leading products:
  - Serotonin Reuptake Inhibitors (SRIs)
    - Market share of approx. 80%
    - Selective Serotonin Reuptake Inhibitors (SSRIs)
      - first line treatment
    - Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
      - fastest growing segment

# Depression Market

- Factors influencing prescribing trends
  - Drug attributes
    - #1: Overall efficacy (33%)
      - No real difference between the SRIs perceived
    - #2: Overall side effect profile (19%)
      - No real difference between the SRIs perceived
  - Generics
    - 80-90% R<sub>x</sub> will be generic when both branded and generic versions of a product are available

# Depression Market

- Life Cycle Management Strategies:
  - New formulations
  - New indications
  - Development of enantiomers/analogues
  - Authorized Generics
  - Own Generics
  - Rebates
  - Price decrease
  - Brand loyalty programs

# Depression Market

- Pipeline Analysis ( $\geq$  phase 1):
  - Total # of compounds in development: 65
  - Total # of SRIs: 13 (20%)
  - Breakdown:
    - Registration: 1 (of which 0 SRIs)
    - Phase 3: 7 (of which 2 SRIs)
    - Phase 2: 28 (of which 5 SRIs)
    - Phase 1: 29 (of which 6 SRIs)

# Depression Market

- Pipeline Analysis ( $\geq$  phase 1):
  - Most targeted neurotransmitters/systems:
    - Serotonin
      - 13 SRIs
      - 11 other serotonin based modes of action
    - HPA-axis
      - 7 CRF-1 antagonists
      - 3 glucocorticoid antagonists
    - Glutamate
      - 5 compounds with 3 different modes of action
    - Neurokinin
      - 2 NK<sub>1</sub> receptor antagonists
      - 2 NK<sub>2</sub> receptor antagonists

# Depression Market

- Unmet Needs:
  1. Improved efficacy
  2. Faster onset of action
  3. Better side effect profile

# Depression Market

- Conclusions:
  - Large attractive market
  - SRIs first line treatment and still making up 20% of the clinical phase antidepressants pipeline
  - Little difference between SRIs with regard to overall efficacy and overall side effect profile as perceived by prescribing physicians
  - Clear need for improved efficacy, faster onset of action and better side effect profile

# ENSPYR Concept

Treatment of depression with an SRI combined with pyridoxine renders:

1. Improved efficacy
2. Faster onset of action
3. Better side effect profile

# ENSPYR Rationale

- Pyridoxine is an important co-factor for serotonin-decarboxylase, an enzyme involved in the last step of serotonin synthesis
- Addition of pyridoxine leads to an increased serotonin production and higher serotonin concentration in the synaptic cleft:
  - Improved efficacy
  - Faster onset of action
  - Better side effect profile (due to lowering of effective dose of SRI)

# Results in Validated Rat Models

- Microdialysis
  - Combining pyridoxine with an SRI leads to higher serotonin concentrations in the brain compared to SRI monotherapy
- Head Twitches
  - Pyridoxine enhances the efficacy of SRIs
- Chronic Mild Stress
  - Combining pyridoxine with an SRI improves efficacy, increases responder rates and shows a faster onset of action compared to SRI monotherapy

# Pharmacological Proof

- Three validated pharmacological animal models for SRI action showed:
  - Compared to SRI monotherapy combination therapy with pyridoxine renders:
    1. Improved efficacy
    2. Faster onset of action
    3. Better side effect profile

# Licensing Proposition

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# Licensing Proposition

- PRB is looking for a strong partner for:
  - Pharmaceutical development
  - Final clinical development and regulatory approval
  - Commercialization
- In case of interest please contact:
  - Pantarhei Bioscience
  - PO Box 464
  - 3700 AL Zeist
  - The Netherlands