

Agomelatine in Innovative Dosage Forms

*Agomelatine Transdermal Therapeutic System (TTS),
Agomelatine Oral Thin Film (OTF)*

for treatment of Major Depressive Disorder

Non-Confidential Information Memorandum

2021



Agomelatine

Attractive Market



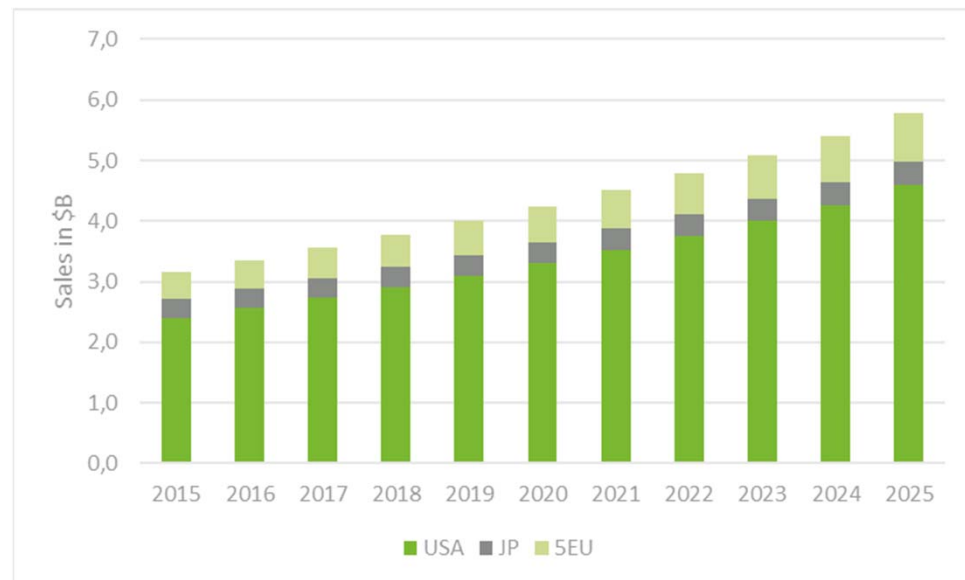
- Depression is a **\$12.6 billion global market** (2018, IQVIA). North America accounts for 44% of revenues.
- Agomelatine is an atypical antidepressant used to treat major depressive disorder, currently available as tablets of 25mg and 50mg (trade names: Valdoxan[®], Melitor[®], Thymanax[®]).
- Agomelatine has a unique receptor binding profile yielding in a **faster onset of action** and **fewer typical side effects** known for antidepressant agents. The current dosage form limits the potential of Agomelatine due to hepatotoxic side effects, low bioavailability and high plasma level fluctuation.

Major Depressive Disorder Market Features



- Estimated 16.2 million adults in the United States had at least one major depressive episode. This number represented 6.7% of all US adults and is majorly prevalent in women as compared to men. While Major Depressive Disorder can develop at any age, the median age at onset is 32.5 years old.
- There are several main significant unmet needs in the depression market:
 - Products with better efficacy
 - Products with improved safety profiles
 - Products with fewer side effects
 - Products with a rapid onset of action

Global Sales by Region for MDD Therapies, 2015-2025



Source: GlobalData

Agomelatine TTS and OTF

Commercial Opportunities in a Large Market

- LTS has developed
 - A <12 hrs **transdermal therapeutic system (TTS)**, and
 - A **transmucosal oral thin film (OTF)** for bedtime administration.

- Encouraging **development milestones** were **achieved** for both, Agomelatine-TTS and Agomelatine-OTF
 - LTS proprietary TrACE[®] analysis tool (in silico evaluation) confirmed **ideal physicochemical properties**.
 - Selected prototypes with very promising flux profile were identified to deliver **sufficient overnight plasma levels** of Agomelatine.
 - Preclinical study using Göttingen minipig was performed with several OTF as well as with TTS formulations showing **excellent tolerability**.

- LTS' main goal is the **removal of the hepatotoxicity** warning (as is for Valdoxan[®]) through significant reduction of the administered Agomelatine dose.

- As one of the next development milestones, LTS is preparing **clinical phase I study**, with commercial launch intended in 2026.

Pharmacological Advantages

Unique benefits of **TTS** include:

- **Constant drug plasma levels** over long duration of action, leading to improved **patient comfort**
- **Lower adverse reactions**
- Improved **patient compliance**

TTS offer alternatives to patients who experience discomfort, swallowing difficulties or undesirable side effects caused by conventional dosage forms.

Pharmacological Advantages

Unique benefits of **OTF** include:

- **Avoidance of the first-pass effect by using transmucosal route**
- **Fast onset of action**
- **Improved bioavailability**
- **Potentially lower amounts of active substances than with tablets or solutions**
- **Controlled application of the required dose**
- **Improved patient compliance**

Agomelatine TTS and OTF



Benefits of new innovative dosage forms

Patients and Caregivers:

- Considerable reduction of the administered dose to remove the hepatotoxicity warning for the oral marketed dosage form.
- Reduction of intra- and interindividual plasma level fluctuations by circumventing the GI-tract passage yielding in a more robust pharmacokinetic profile with increased bioavailability (current bioavailability of the oral marketed dosage form: 1-5%).
- Avoidance of food impact and reduced interaction with co-medications (especially estrogen treatment of women).
- Strengthen of the overall unique mechanism of action of Agomelatine addressing current unmet needs in the treatment of depression due to faster onset of action and lower side effects of the compound itself (mainly less weight gain and less sexual dysfunction compared to other antidepressant agent).

To Licensees of the Products:

- Technically well-designed; NDA regulatory pathway for new exclusive US market entry in 2026
- Attractive market potential

LTS: Transdermal Innovator

12 active substances have been brought to market by LTS' commercial partners, among which are:

- **Neupro[®]** (rotigotine) Parkinson's disease
- **Exelon[®]** (rivastigmine) Alzheimer's disease
- **Deponit[®]** (nitroglycerine) Angina pectoris
- **Matrifen[®]** (fentanyl) Severe pain
- **Habitrol[®]** (nicotine) Smoking cessation
- **Evra[®]** (ethinyl estradiol/norelgestromin) Contraception
- **Estraderm[®]** (estradiol) Menopausal symptoms
- **Butrans[®]** (buprenorphine) Moderate to severe pain

LTS
Account
Team

LTS: Oral Thin Film Innovator

- Pioneer in OTF with **LISTERINE POCKETPAKS®** Oral Care Breath Strips and other OTC and consumer products
- First generic Suboxone® **Buprenorphine and Naloxone Sublingual Film** for the treatment of opioid use disorder and addiction
- **SETOFILM®** ondansetron oral dispersible film - prophylaxis of acute nausea and vomiting induced by moderately emetogenic chemotherapy
- **Breakyl®** (fentanyl) buccal soluble film for the treatment of breakthrough cancer pain
- Innovative OTF pipeline with partnered projects in various indications
- Portfolio of formulation, process and packaging patents

NEXT STEPS AND CONTACT INFORMATION

To receive further information, interested parties will need to sign a CDA to access the Confidential Information describing the Agomelatine TTS and/or Agomelatine OTF opportunity.

For further information, please contact:

Dr. Stefan Arnold

Director Business Development Asia -
Representative Asia
LTS Lohmann Therapie-Systeme AG

Asia Office
29/F Gopher Center
No. 757 Mengzi Road, Shanghai 200023
P.R. China
Phone.: +86 21 3858 5232
Mobile: +86 185 2105 8711
Stefan.Arnold@ltslohmann.de