

# Aripiprazole Oral Once-Weekly

*Executive Summary*

The logo for Zysis, featuring the word "Zysis" in a white, cursive script font with a registered trademark symbol (®) to the upper right. The background of the entire page is a solid blue color with decorative white lines: a thick, wavy line and several thinner, straight lines that create a sense of movement and depth.

## Summary

The total market that an oral, once-weekly, patent-protected formulation of aripiprazole can target is 13.4 billion USD; Zysis forecast a 5.5% market share by value, creating peak year sales of 600–1000 million USD (70% US, 15% EU, 15% RoW).

An FDA New Drug Application submission is anticipated within 3 years, with a total investment of only 23 million USD for clinical trial work required to reach this point.

This is a low risk project; although it would become a novel, unique therapy in the antipsychotic market (an oral once-weekly), it is still a reformulation and, as such, has >75% chance of achieving approval with no unknown serious events likely to emerge in the future – aripiprazole oral once-daily has been on the market since 2001, and has been prescribed to many millions of patients.

## Introduction

Zysis is a privately-owned specialty pharmaceutical company optimising therapies for disorders of the central nervous system (CNS). Zysis has reformulated aripiprazole, an effective antipsychotic molecule, to provide a patent-protected, sustained-release, once-weekly maintenance phase therapy in oral tablet form to improve clinical outcomes in schizophrenia and bipolar disorder therapy. Adherence to treatment is the major issue in the management of both schizophrenia and bipolar disorders from the patient, carer and healthcare provider perspective. This new treatment paradigm will dramatically reduce the costs associated with symptom relapse from non-adherence, such as rehospitalisation, as well as benefit other community costs, including community-based nurses having to visit patients daily. Observed dosing on a weekly basis becomes a real option for many more patients than would be possible with existing daily therapies. Formulation development and initial Phase I studies have been successfully completed, the Phase II clinical program has been established and Zysis wishes to partner this development product going forward.

## Background

Aripiprazole (brand name Abilify®) is an excellent atypical antipsychotic with a unique partial agonist mode of action. It currently achieves approximately 3.4 billion USD sales per year worldwide and is still rapidly growing, with an approximate 75% of total antipsychotic sales in the US. Aripiprazole is approved for acute and chronic treatment of schizophrenia and schizoaffective disorders, and for the treatment of manic symptoms associated with bipolar disorders. Trials in bipolar depression were discontinued due to lack of efficacy. More recently, aripiprazole has received further indications as an adjunctive treatment for major depressive disorder, and for the treatment of irritability associated with autism.

The drug is currently provided to patients in several formulations; oral immediate release (IR) tablet, oral disintegrating tablet, oral solution, and intramuscular (IM) injection, with the oral IR tablet being the most commonly prescribed. In addition, there are long-acting depot injection formulations in development by Otsuka and Alkermes. Otsuka is not developing any alternative oral formulations at present, having decided to focus CNS development activities on pipeline new chemical entities (NCEs).

## Opportunity

Zysis has successfully formulated a sustained-release once-weekly oral version of aripiprazole (aripiprazole oral OW) by targeting specific characteristics of the drug molecule. The long plasma elimination half-life of 72 hours allows for extended drug residence in the systemic circulation. In addition, and more importantly, recent positron emission tomography (PET) imaging studies have demonstrated that, in schizophrenia patients, aripiprazole remains bound to the dopamine D2/D3 receptors in the brain for a prolonged period of time, even when the plasma levels have declined significantly; the extent of the brain and plasma pharmacokinetic disconnect is unique to aripiprazole opening up the prospect of once-weekly maintenance therapy.

Human pharmacokinetic 'proof of principle' studies on sustained-release prototype formulations have been undertaken, and the resulting data utilised to model the steady-state characteristics at a variety of doses and dosing frequencies, indicating that the development objectives of Zysis are achievable. In addition, 18-month International Conference of Harmonization (ICH) stability data show no change in drug release properties or related substances for the aripiprazole sustained-release platform.

Other long-acting formulations of antipsychotics are IM injections, and therefore reserved for severe cases, whereas aripiprazole oral OW can also be targeted at patients with mild-to-moderate symptoms but who are struggling to adhere to once-daily therapy. Non-adherence is the main issue in schizophrenia treatment at present; within 2 years of leaving hospital, approximately 75% of patients will have become non-adherent, and 69% of these patients will be rehospitalised.

Features of a once-weekly oral formulation of aripiprazole include substantially reduced oral dosing frequency, and an oral maintenance product instead of a depot injection maintenance product. The key benefits that therefore ensue are:

- The opportunity for observed dosing, and therefore high levels of adherence, to become a real option for many more patients than currently
- The opportunity for patients to be released from the stigma and association of taking daily therapy; for young patients and first-episode patients, this is a major issue and can often result in non-adherence to therapy
- Patients struggling to adhere to oral daily therapy could have a new option instead of stepping to injectable depot products
- An oral, maintenance, adherence-enhancing product, even in an observed dosing scenario, has a direct cost benefit over depot injections, and indirect cost benefits over all oral once-daily therapies

Improvements in health economic outcomes generated by better adherence will enable the marketer of aripiprazole oral OW to achieve a price for the product that approaches the current weekly cost of Abilify, despite the presence of generic once-daily aripiprazole.

The maintenance segment of the antipsychotic market has been estimated to be as much as 85% of patients, worth approximately 11 billion USD at present. Within that segment, aripiprazole oral OW has the potential to target all patients as an adherence-improving product, not just the patients who would be selected for treatment with current formulations of aripiprazole. It would rapidly become the product of choice for non-adhering patients (75%) whilst also offering a more convenient alternative for adhering patients (25%). Stepwise promotion of the product to achieve maximum market share is

recommended, focusing on a series of sub-segments at first, to ensure fast uptake and familiarisation by all psychiatrists, plus associated disciplines such as psychogeriatricians, first-episode/adolescent and forensic psychiatry.

Current patent protection for aripiprazole runs until 2014 in the EU and 2015 in the USA. Prosecution of the patent covering the Zysis once-weekly oral version of aripiprazole in the key markets (USA, Europe, Japan, Israel, Australia, Canada and South Korea) is progressing very well, and a favourable examiner report has recently been received from the European Patent Office.

The antipsychotic market is a specialist market (psychiatrists) making targeted promotion possible, and Key Opinion Leader (KOL) influence in this market is therefore particularly strong. Zysis has sought significant KOL scrutiny on the aripiprazole oral OW concept, and is very encouraged by the feedback received so far:

*‘Actually, I think this treatment would be very useful for a substantial population of patients, especially bipolar ones for whom no long-acting preparation is licensed in France.’*

**Professor Jean-Michel Azorin**

Marseilles, France

*‘Adherence is one of the most important problems with antipsychotic treatment, and it is very difficult to be sure if patients take the prescribed oral medications. In addition, there are a proportion of patients that do not like injectable preparations. Once a week is a very friendly way of taking a drug and family can easily control the intake of medication if needed.’*

**Professor Maria-Luisa Figueira**

Lisbon, Portugal

*‘I think the possibility of a once-weekly oral medication would be a great boon for early psychosis and for all patients. Very exciting and hopefully not too good to be true!’*

**Professor Pat McGorry**

Melbourne, Australia

*'Aripiprazole has both a different mechanism and a much broader spectrum of action (depression, mania and antipsychotic) so the population that is likely to be considered for this drug is larger than the typical antipsychotics. Even if there are no studies done for patients from these diagnostic categories, it is likely that physicians will use it in that way anyway, since it is known to work for those illnesses. So, I think that there is a significant population that could benefit from this new drug.'*

**Dr. Richard McCarthy**

New York, US

*'Adherence is an important issue for clinical practice. Aripiprazole once-weekly could be particularly useful for patients with partial adherence, or in order to simplify drug administration in non-adherent patients.'*

**Professor Giulio Perugi**

Gerona, Italy

*'Very long-acting oral formulations of antipsychotic medications are desperately needed. Most of the patients are non-compliant most of the time, which is why they are forever relapsing and requiring readmission, crisis and intensive home treatment, etc.'*

**Professor Ann Mortimer**

Hull, UK

*'Yes, adherence or non-adherence is a major problem and we have been doing a lot of work on this issue lately. The potential pool includes all of those that you have indicated.'*

**Professor Ashok Malla**

Montreal, Canada

*'Adherence is a big issue and contributes significantly to poorer outcomes in schizophrenia and bipolar disorder. I agree that the potential market for a weekly oral antipsychotic would likely be significant, and that an accompanying "compliance" package would be a good thing to think of.'*

**Professor Allan Young**

London, UK

*'I agree on the potential target population and would like to remark that, besides the non-adherent patients who can be as many as 40% of bipolar patients (similar in schizophrenia) or even more in some settings, there are also those patients who are "potential candidates for non-adherence". Those are patients who may be taking the medication today but might change their mind in the future. Rates are then much higher than 40% and up to 80%.'*

**Professor Eduard Vieta**

Barcelona, Spain

*'Sounds a good product, non-compliance is a huge issue; anything that helps is a good thing. If it works then why would any patient take daily meds? If people could take a lipid-lowering drug once a week rather than daily then most, if not all, would. I see a lot of refractory patients so aripiprazole OD isn't used as much, but in general psychiatry I would be tempted to try it in most people that I would be happy putting on aripiprazole; so around 30–40%. And perhaps more in first-episode patients, as I would like the idea of low metabolic and EPS side effects.'*

**Professor Sukhi Shurgill**

London, UK

## Conclusion

Aripiprazole oral OW is a simple step to better treatment outcomes in schizophrenia and bipolar disorders. It offers a new treatment paradigm in the therapy of both conditions, and a new hope for the 75% of patients who struggle to adhere to existing therapies. A once-weekly oral formulation of aripiprazole will represent a significant, unique and welcome advance in antipsychotic therapy, and is expected to capture a substantial share of the market.

ProPharma Partners is assisting Zysis in identifying potential partners.

For further information on this opportunity please contact:

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