

**Economic evaluation of Agomelatine (Valdoxan®) for the treatment of  
major depressive disorder**



## Summary

1. The cost effectiveness of agomelatine for the treatment of major depressive disorder was reviewed following the receipt of a reimbursement dossier from Servier Laboratories Ireland in April 2009. Following the initial evaluation further documentation was submitted in June and July 2009.
2. Agomelatine is the first melatonergic antidepressant, being an agonist at MT<sub>1</sub>/MT<sub>2</sub> receptors and an antagonist at 5-HT<sub>2c</sub> receptors. Agomelatine increases dopamine and noradrenaline in the frontal cortex without altering serotonin levels. It received EU market authorisation in February 2009 for the treatment of major depressive episodes in adults.
3. The economic evaluation was based on a number of agomelatine trials including studies 035, 041, 036 and study 030. Further data was provided from studies 045 and 046. Data from three “failed” studies i.e. 022, 023 and 024 were excluded from this submission. A number of explanations were offered (by the manufacturer) as to why these non-conclusive or failed studies were not included in the economic analysis. Firstly, the trials were methodologically compromised making the results impossible to interpret. It was suggested that these non-conclusive short-term trials were not designed to show differences between the active treatment but to demonstrate agomelatine’s antidepressant effect. Finally, more robust data evaluating the clinical efficacy of agomelatine versus SSRI and SNRI treatments was available and therefore was used in the pharmacoeconomic evaluation. The review group considered that the omission of non-conclusive or failed studies could have introduced bias in favour of agomelatine.
4. In the GMS basecase analysis from the HSE perspective agomelatine dominated placebo. The ICER’s in relation to the comparators were as follows: venlafaxine €25,389/QALY, fluoxetine €11,850/QALY, paroxetine €6,316/QALY and sertraline €3,771/QALY. Corresponding figures from the Drug Payments scheme confirm that placebo was dominated by agomelatine and the ICER’s in relation to

comparators were as follows: venlafaxine €7,182/QALY, fluoxetine €18,600/QALY, paroxetine €10,514/QALY and sertraline €6,690/QALY. From a societal perspective agomelatine dominated all comparators.

5. In the July 2009 submission data from two new randomised controlled trials comparing agomelatine versus fluoxetine and sertraline (studies 045 and 046) provided more favourable ICER values e.g. agomelatine versus venlafaxine €7,960/QALY, fluoxetine €4,091/QALY, paroxetine €2,188/QALY and sertraline €3,448/QALY (GMS scheme, HSE perspective). Corresponding values for the Drug Payment scheme (HSE perspective) were as follows: venlafaxine €13,280/QALY, fluoxetine €9,545/QALY, paroxetine €4,406/QALY and sertraline €4,586/QALY. In the revised analysis agomelatine dominated all comparators when the societal perspective was considered.
6. The ICER value appeared particularly sensitive to the simulation period, change in the price of agomelatine and the risk of remission for the comparator drugs on sensitivity analysis. Alteration in the risk of remission for the comparator drugs resulted in large changes in the ICER value e.g. agomelatine vs. paroxetine (GMS/HSE perspective) the ICER was €1,041/QALY when the risk of remission was 17.9%, however paroxetine was dominant when the risk of remission was 32.8%. Similar findings were noted for other comparators.
7. Acceptability curves for agomelatine vs. comparators under the GMS scheme from the societal perspective indicated that agomelatine is cost effective in 85.7% to 90.5% of cases. For agomelatine vs. venlafaxine under the GMS scheme from the HSE perspective the probability of agomelatine being cost effective was 82.7% at a threshold of €45,000/QALY. The probability of agomelatine being cost effective (vs. venlafaxine) fell to less than 30% if a threshold of €20,000/QALY was applied. As expected the probability of cost effectiveness of agomelatine was lower under the Drug Payment scheme and vs. venlafaxine was 63.8% at the €45,000/QALY threshold. However this fell to less than 10% for a

threshold of €20,000/QALY. Similarly vs. fluoxetine the probability of cost effectiveness was 76.2% for a threshold of €45,000/QALY falling to approximately 50% at the €20,000/QALY threshold level.

8. The price of agomelatine is significantly higher than comparators such as fluoxetine, paroxetine and venlafaxine. The combined five-year budget impact for agomelatine under the GMS and DP schemes was estimated at €1.9million with a range of €1.5million to €2.2million. The review group considered that the sensitivity analysis demonstrated uncertainty in the ICER calculations and the significant reduction in the probability of cost effectiveness for agomelatine at lower threshold levels. We are not convinced that agomelatine represents value for money at the current price. The submitted data suggests that there may well be a place for agomelatine in the treatment of major depressive episodes in adults however the pricing of this product under the community drugs schemes should be reconsidered.