TECHBRIEF

HORIZON SCANNING REPORT

TOLUDESVENLAFAXINE HYDROCHLORIDE (LY03005) FOR MAJOR DEPRESSIVE DISORDER

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MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

"DOKUMEN TERHAD"

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EXECUTIVE SUMMARY

Major depressive disorder (MDD) is a common but complex illness, with a variety of unique symptom combinations such as low mood, loss of interest, difficulty in concentrating, sleep disturbances, fatigue, and in more severe form, functional impairment and suicidal thoughts. Toludesvenlafaxine hydrochloride is a serotonin–norepinephrine–dopamine reuptake inhibitor (SNDRI). Early evidence of phase III clinical trials was found to improve the severity symptoms of depression, suggesting its potential as a treatment option for individuals with MDD while maintaining good tolerability supporting further investigation to observe the safety and economic impact on the patients.

Keywords: Toludesvenlafaxine hydrochloride, LY03005, major depressive disorder, functional impairment

INTRODUCTION

The World Health Organization (WHO) has ranked depression as the 4th leading cause of disability worldwide, with projections indicating that it will become the second leading cause by 2030.[1] In terms of global disease burden measured in disability-adjusted life years, MDD increased by 37% between 1990 and 2010 and is projected to become the single leading cause of disease burden by 2030 in high-income countries.[2,3] There are approximately 350 million individuals with MDD worldwide and it is projected to be a top contributor to global functional disability in the following decades.[4] In a systematic review that includes 63 articles, the lifetime prevalence of MDD ranged from 2 to 21%, with the highest rates found in some European countries and the lowest in some Asian countries.[5]

A review of depression studies in Malaysia showed the prevalence of MDD in Malaysia to was between 8 - 12%.[6] A meta-analysis showed a global prevalence of MDD at 4.7% (95% CI 4.4 to 5.0%).[7] According to a study on the burden of depressive disorders by country, MDD is a substantial contributor to disability-adjusted life years (DALYs) in Malaysia, impacting the country's socioeconomics.[8] The National Health and Morbidity Survey (NHMS) 2019 found that the prevalence of depression was 2.1% among those aged 15 to 19 years old.[6] Furthermore, the burden of depression among the elderly in Malaysia has been highlighted, with reported prevalence rates ranging from 6.3% to 18.0%.[9,10] Additionally, depression has been associated with various factors such as self-esteem, lifestyle, and emotional disorders among different population groups in Malaysia, including school-going adolescents,[11] university students,[12] and the elderly.[10] The prevalence of depression among patients in primary care centers, clinical settings, and the general community in Malaysia has been reported to range from 6.7% to 14.4%.[13]

Therefore, effective MDD treatment is warranted as it may have a substantial effect on reducing its global impact on individuals, families, and society at large.

THE TECHNOLOGY

Toludesvenlafaxine hydrochloride (LY03005) formerly known as Ansofaxine is a new chemical entity that works as a triple reuptake inhibitor of serotonin, norepinephrine, and dopamine (SNDRI) intended for the treatment of major depressive disorder (MDD).[14] This drug is a carboxylic acid ester prodrug to desvenlafaxine and is administered as an oral extended-release tablet.[14] The mechanism of action involves its role as a triple reuptake inhibitor of serotonin, norepinephrine, and dopamine.[14] This mechanism is similar to the monoamine hypothesis of depression, which suggests that dysregulation of these neurotransmitters is involved in the pathophysiology of depression.[14]

The development of toludesvenlafaxine hydrochloride for major depressive disorder is attributed to Luye Pharma, as it was developed under their new chemical and therapeutic entities research and development platform.[15] In the United States, Europe, and Japan, toludesvenlafaxine is preregistered for the treatment of depression as of July 2018.[15] It is presently undergoing phase 3 clinical studies for the treatment of generalised anxiety disorder as of January 2023.[15] The New Drug Application for toludesvenlafaxine was submitted to the US Food and Drug Administration (FDA) in 2020; and is currently undergoing evaluation.[15] Toludesvenlafaxine was authorised for the treatment of depression in China in November 2022 under the brand name Ruoxinlin.[16]

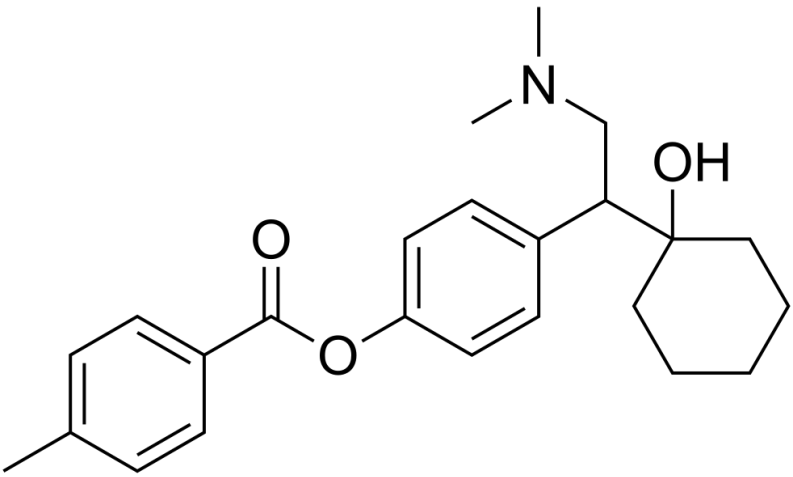

Figure 1: Chemical structure of toludesvenlafaxine[17]

PATIENT GROUP AND INDICATION

Toludesvenlafaxine hydrochloride is indicated for adult patients with major depressive disorder. The mechanism of action of triple reuptake inhibitors involves blocking the reuptake of serotonin, norepinephrine, and dopamine, leading to increased extracellular concentrations of these neurotransmitters and prolonged synaptic activity.[17] This unique mechanism offers a promising approach to treat depression by modulating multiple monoaminergic pathways simultaneously.[17]

CURRENT PRACTICE

According to the Malaysian Clinical Practice Guidelines on the Management of Major Depressive Disorder (Second Edition), the severity of MDD should be assessed to determine the mode of treatment screening.[1] Whooley Questions may be considered as a screening tools for people at risk in primary care.[1] Psychoeducation should be offered early and continuously throughout the management of major depressive disorder.[1]

In mild to moderate major depressive disorder, psychosocial intervention, and psychotherapy should be offered, based on resource availability, but not restricted to cognitive behavioural therapy, interpersonal therapy, problem-solving therapy, behavioural therapy, and internet-based cognitive behavioural therapy.[1] In moderate to severe major

depressive disorder, a combination of pharmacotherapy and psychotherapy should be offered while exercise may be offered as an adjunct treatment.[1] In moderate to severe major depressive disorder, second-generation antidepressants that should be prescribed include selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, melatonergic agonist and serotonergic antagonist, multimodal serotonin modulator and noradrenaline/dopamine-reuptake inhibitor.[1]

In the maintenance and continuation phase, antidepressants should be continued for at least six to nine months after remission, and at least two years if there is a high risk of relapse or recurrence.[1] A combination of antidepressants and antipsychotic should be considered in major depressive disorder with psychotic features.[1] Optimisation of antidepressants should be considered in patients who fail to show response to initial treatment in major depressive disorder.[1] If optimisation fails, patients should be referred to a psychiatrist for switching or combination or augmentation options.[1]

Besides that, electroconvulsive therapy may be considered in MDD patients with life-threatening conditions such as refusal to eat and high suicidality, moderate to severe symptoms for rapid improvement in the acute treatment, and treatment-resistant depression.[1]

EFFICACY AND SAFETY

There were three articles included which were retrieved from the scientific databases (Medline, EMBASE, PubMed), the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] and from the references of retrieved articles. The search was conducted up to 4 Mac 2023. The three retrieved evidence included two completed clinical trials and a systematic review of novel antidepressants in the US clinical trials registry.

The results of the phase II and phase III clinical trials of toludesvenlafaxine (LY03005) for the treatment of major depressive disorder (MDD) were reported in a multicenter, randomised, double-blind, placebo-controlled, dose-finding phase II clinical trial and a phase III, multicenter, double-blind, randomised, placebo-controlled clinical trial, respectively.

A phase III clinical trial was conducted at 22 centers in China from December 2018 to December 2020 to verify the efficacy and safety of toludesvenlafaxine in 558 adult patients with MDD.[18] Patients were randomised to receive toludesvenlafaxine 80 mg/day, 160

mg/day, and placebo respectively.[18] Among 558 patients, 552 were included in the full analysis set. The primary efficacy endpoint was the change of the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to the end of week eight.[18] Secondary efficacy endpoints were the changes from baseline of the following scores at the end of week eight: Hamilton Rating Scale for Depression-17 item (HAMD-17)] total score; Clinical Global Impressions-Improvements (CGI-S score); Hamilton Anxiety Rating Scale (HAMA) total score and Sheehan Disability Scale (SDS) total score.[18] After 8 weeks of treatment, both dosages of toludesvenlafaxine were statistically significantly superior to placebo in the adjusted mean changes from baseline in the MADRS total score with the least squares mean (LSM) difference to placebo of −5.46 [toludesvenlafaxine 80 mg/day, (95% CI: (−7.14 to −3.77)), $p < 0.0001$] and −5.06 [toludesvenlafaxine 160mg/day, (95% CI: (−6.75 to −3.37), $p < 0.0001$].[18] Significant differences versus placebo were consistently observed across secondary and additional efficacy measures in treatment groups.[18] The adjusted mean changes from baseline in the HAMD-17 total score were significantly higher in subjects administered with toludesvenlafaxine 80 and 160 mg than in those administered with placebo after 8 weeks of treatment.[18] The LSM difference to placebo was −3.57 [(95% CI: (−4.87 to −2.27), $p < 0.0001$)] for toludesvenlafaxine 80 mg/day group and −3.24 ([95% CI: (−4.54 to −1.94), $p < 0.0001$)] for toludesvenlafaxine 160 mg/day group at the end of week 8.[18] A statistical significance was observed in the mean changes of CGI-S score, HAMA total score, and SDS total score from baseline for both dosages of toludesvenlafaxine versus placebo ($p < 0.05$).[18] In short, the results of this trial demonstrate both dosages of 80 mg and 160 mg of toludesvenlafaxine were effective and clinically significant compared to the placebo group.

In terms of safety, treatment-emergent adverse events (TEAEs) were reported by 137 (74.4%) patients in the toludesvenlafaxine 80 mg group, 144 (78.2%) patients in the toludesvenlafaxine 160 mg, and 125 (67.9%) patients in the placebo group.[18] Most TEAEs were mild or moderate in severity.[18] Fourteen subjects had severe TEAEs, reported by 4 (2.1%, 5 events), 4 (2.1%, 6 events), and 6 (3.2%, 8 events) in the toludesvenlafaxine 80 mg, toludesvenlafaxine 160 mg, and placebo groups, respectively.[18] A total of 31 subjects withdrew from the trial due to TEAEs; 25 out of the 31 subjects withdrew from the trial due to the study drug as judged by the investigator, including seven patients (3.8%) in the 80 mg toludesvenlafaxine group, thirteen patients (7.1%) in the 160 mg toludesvenlafaxine group, five patients (2.7%) in the placebo group.[18] The incidence of treatment-related adverse events (TRAEs) was reported to be 59.2% (109 cases, 233 events), 65.2% (120 cases, 296 events), and 45.1% (83 cases, 170 events) in toludesvenlafaxine 80mg, 160mg, and placebo groups, respectively.[18] The most common three TRAEs in toludesvenlafaxine groups were nausea, dizziness, and dry mouth, of which the incidence of nausea and dry

mouth was higher in the 160 mg group vs. 80mg group, whereas the incidence of dizziness was lower in the 160 mg group vs.80 mg group.[18] No death and newly developed sexual dysfunction were reported in this trial. In comparison with other common antidepressants, toludesvenlafaxine showed better safety and tolerability.[18,19,20] The adverse reactions were similar in patterns to those reported with selective serotonin reuptake inhibitors (SSRI's) and serotonin and norepinephrine reuptake inhibitors (SNRI's).[18,21] Both dosages of ansofaxine used in this trial were safe, generally well tolerated and remarkably effective at a clinically relevant level for the treatment of MDD.

In the phase II clinical trial which conducted in ten hospitals in China to determine the effective dose, efficacy, safety, and tolerability of toludesvenlafaxine in 255 MDD adult patients were included.[22] Patients received the study drug as follows; 40 mg (n = 52), 80 mg (n = 52), 120 mg (n = 51), and 160 mg (n = 51) toludesvenlafaxine and placebo (n = 49).[22] The primary outcome was a change in total score on the 17-item Hamilton Depression Scale (HAMD-17) from baseline to week six.[22] Mean changes from baseline in HAMD-17 total scores at week six were −9.71, −12.53, −12.84, −12.14, and −13.56 in the placebo and 40, 80, 120, and 160 mg/d of ansofaxine groups, respectively.[22] The differences among the 5 treatment groups were statistically significant (ANCOVA, $\chi 2 = -9.71$, $p = 0.0447$).[22] Adjusted mean differences in HAMD17 total scores (95% CI) that were obtained by comparing placebo with the four toludesvenlafaxine dose groups were statistically significant (−2.92 [−6.09 to 0.24] for the 40-mg group, −3.08 [−6.22 to 0.05] for the 80-mg group, −2.43 [−5.56 to 0.70] for the 120-mg group, and −3.69 [−6.85 to −0.52] for the 160-mg group).[22] At the end of week 6, mean changes in secondary endpoints of Hamilton Anxiety Rating Scale (HAMA) total scores, the HAMA somatic anxiety factor, and the HAMD17 anxiety factor were significantly higher for three of the ansofaxine groups (40, 80, and 160 mg/d) but not for the 120-mg ansofaxine group compared to placebo. Clinical Global Impressions-Improvements (CGI-I) scores were significantly higher in all ansofaxine groups than in the placebo group.[22] However, no significant differences were observed among the five groups in Visual Analog Scale of Pain Intensity (VAS-PI) scores.[22] Overall, results showed that toludesvenlafaxine was superior to placebo in all four dose groups.

Meanwhile, the incidences of TRAEs in the 40, 80, 120, and 160-mg/d toludesvenlafaxine groups were 51.92%, 65.38%, 56.86%, and 62.75%, respectively.[22] The percentages of withdrawal that were attributable to adverse events (AE) were 1.92%, 7.69%, 7.84%, and 9.80% in the 40, 80, 120, and 160-mg/d toludesvenlafaxine groups.[22] As the incidences of AEs and rate of discontinuation attributable to AEs of ansofaxine were similar to SSRIs and lower than SNRIs, suggesting that the safety and tolerability of toludesvenlafaxine were similar to these SSRIs and better than other SNRIs.[22, 21] Most AEs that occurred were mild

to moderate, with no unexpected adverse reactions.[22] The most common AEs that were related to the study drug (>5% incidence and twofold higher incidence vs placebo) were nausea, lethargy, decreased appetite, and dry mouth, which were similar to SSRIs and SNRIs.[22, 21] Two serious adverse events occurred in the 40-mg/d ansofaxine dose group, namely hypomania (mild) and the exacerbation of depression (severe), which were determined to be related to toludesvenlafaxine and stable during follow-up.[22] Notably, throughout the whole trial, only 1 case reported sexual dysfunction in the 80-mg ansofaxine group.[22] Thus, in this trial all active doses of ansofaxine were reported to be safe and well tolerated.

ESTIMATED COST

There was no retrievable evidence on the exact cost and economic assessment of toludesvenlafaxine. The manufacturers have not announced the treatment's price.

However, the cost for desvenlafaxine oral tablet, extended release (50 mg) is around 71 USD (MYR 330.33; 1 USD = MYR 4.65) for a supply of 30 tablets, depending on the manufacturers.[23]

POTENTIAL IMPACT

Overall, early evidence showed that the extended-release tablet of toludesvenlafaxine hydrochloride may be a potential treatment option for managing MDD as the trials showed good efficacy and tolerability. However, larger samples and longer clinical trials are needed to establish its safety and efficacy.

A full economic evaluation will be needed to determine the cost-effectiveness and affordability of incorporating toludesvenlafaxine hydrochloride into the current treatment strategies.

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