TECHBRIEF

HORIZON SCANNING REPORT

CENTANAFADINE IN ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Report No: 006/2024

MAHTAS
MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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EXECUTIVE SUMMARY

Attention-deficit hyperactivity disorder (ADHD) is a long term condition of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. Although current treatment may reduce symptoms and improve functioning, different therapeutic approaches are warranted to improve the management of ADHD with favourable safety and tolerability. Centanafadine is a sustained-release tablet that has been investigated for the treatment of ADHD in adults. It is a stimulant with non-stimulant properties that inhibits the reuptake of norepinephrine, dopamine, and serotonin in the ratios of 1:6:14, respectively. Early studies showed that centanafadine is effective in improving the symptoms and is well tolerated.

Keywords: centanafadine, attention-deficit hyperactivity disorder

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), ADHD is a common neurodevelopmental disorder characterised by symptoms of inattention, hyperactivity, and impulsivity.[1] Studies have shown that ADHD prevalence estimates vary across populations.[2] The burden of ADHD is not limited to childhood, as it can persist into adulthood, albeit with declining prevalence rates.[3] Attention-deficit hyperactivity disorder in adulthood may impose a considerable burden throughout a patient's life as this group of patient are more likely to be unemployed and have a higher rates of mental health impairments than those without the disorder.[4,5] Factors contributing to the occurrence of ADHD are multifactorial, with no single risk factor being necessary or sufficient to explain its occurrence.[6]

Cortese et al reported that the prevalence of symptomatic adult ADHD was 6.76%, and persistent adult ADHD was 2.58%, respectively after adjusting the global demographic in 2020.[7] Globally, there were 139.84 million and 366.33 million affected adults in 2020.[7] In 2019, global burden of disease (GBD) estimated global age-standardized incidence and prevalence of ADHD across the lifespan at 0.06% (95%UI ; 0.040–0.087) and 1.13% (95% UI ; 0.83–1.49), respectively.[8] Attention-deficit hyperactivity disorder accounted for 0.80% of the global mental disorder disability-adjusted life years (DALYs), with mortality set at zero by the GBD.[8] There was a decrease of −8.75% in the global age-standardized prevalence and of −4.77% in the global age-standardized incidence from 1990 to 2019.[8] The largest increase in incidence, prevalence, and burden from 1990 to 2019 was observed in the United States and the largest decrease occurred in Finland.[8] Incidence, prevalence, and DALYs remained approximately 2.5 times higher in males than females from 1990 to 2019.[8] Incidence peaked at age five to nine years, and prevalence and DALYs at age 10–14 years.[8] The reanalysis data before 2013 showed a prevalence in children/adolescents two-fold higher (5.41%, 95% CI; 4.67–6.15%) compared to the corresponding GBD estimated prevalence (2.68%, 95% CI; 1.83–3.72%), with no significant differences between low, middle and high-income countries.[8]

Based on National Health and Morbidity Survey (NHMS) 2015, the estimated prevalence of childhood ADHD was 5.29%.[9] According to study conducted by Gomez et al in 2011, the prevalence of ADHD in Malaysia has been reported to be 2.75% in boys and 0.6% in girls.[10] A cross-sectional study in a Malaysia mental hospital conducted in 2019 involving 120 patients admitted, there were 25% of the patients had a history of childhood ADHD.[11] The prevalence of adult ADHD was 15.8% and the persistence rate was 6.3%.[11] Among the 19 participants with adult ADHD, the most common psychiatric comorbidities were substance dependence (68.4%), lifetime depression (63.2%), and generalised anxiety disorder (47.4%).[11] Compared with participants without ADHD, participants with adult ADHD were less likely to be married (0% vs 21.8%, p = 0.022) and more likely to have alcohol abuse (15.8% vs 2%, p = 0.028), lifetime manic/hypomanic episodes (42.1% vs 7.9%, p = 0.001), and generalised anxiety disorder (47.4% vs 19.8%, p = 0.017), and were younger at first offense (21.8 years vs 26.9 years, p = 0.021).[11]

In short, the prevalence, impact, associated factors, and comorbidities of ADHD demonstrated that effective approaches for effective management with better adverse effect, and support of individuals with ADHD are warranted in Malaysia.

THE TECHNOLOGY

Centanafadine (EB-1020) is a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI) developed for the treatment of attention deficit hyperactivity disorder (ADHD).[12] It inhibits the reuptake of norepinephrine, dopamine, and serotonin with a ratio of 1:6:14, respectively, and is a stimulant with non-stimulant characteristics.[12] The route of administration of centanafadine is orally.

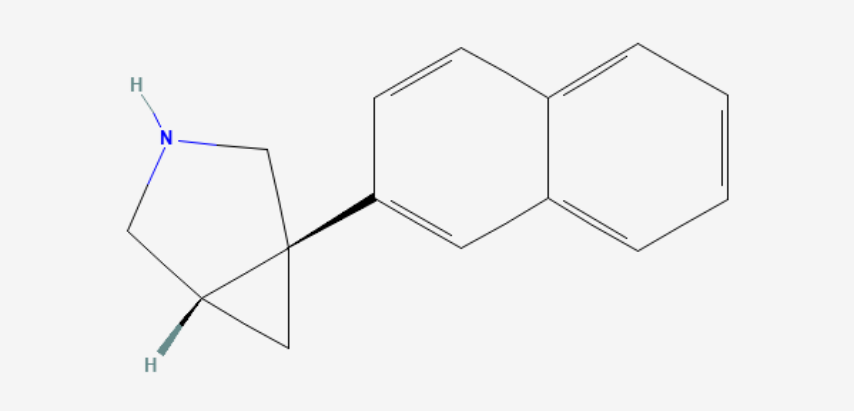

Figure 1: Chemical structure of centanafadine[12]

In 2011, Euthymics Bioscience spun off its development of centanafadine to a new company called Neurovance.[13] In March 2017, Otsuka Pharmaceutical acquired Neurovance and the rights to centanafadine.[14]

PATIENT GROUP AND INDICATION

Centanafadine is indicated for adults with ADHD which has a different mechanism of action than stimulants. It is a sustained release formulation that acts by inhibiting the reuptake of norepinephrine, dopamine, and serotonin.

CURRENT PRACTICE

According to the Malaysian Clinical Practice Guidelines on the Management of Attention Deficit Hyperactivity Disorder (Second Edition), ADHD has a multifactorial and complex aetiology that includes both biological and environmental factors.[15] Attention-deficit hyperactivity disorder is diagnosed based on diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), or hyperkinetic disorders from the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[15] Children and adolescents with signs and symptoms suggestive of ADHD should be referred for assessment and further management. ADHD children

should also be evaluated for comorbidities.[15] The treatment includes psychoeducation, non-pharmacological, and/or pharmacological approaches.[15]

Nevertheless, according to Weibel et al, there were several practical considerations for managing ADHD in adults.[16] The care provision should be multimodal, based on non-pharmacological interventions, and completed by pharmacological treatment in certain conditions.[16] The first objective is to reduce the functional impairment arising from ADHD and associated disorders by offering psycho-education, cognitive-behavioral therapy, and adaptive measures in the workplace.[16] The treatment also aims to directly improve symptoms using other strategies such as cognitive remediation or a pharmacological treatment such as methylphenidate when psychological, educational, social, and family interventions are insufficient.[16]

The National Institute for Healthcare and Excellence (NICE) 2018 (updated 2019) guidelines suggested that after the environmental modifications (e.g., lowering noise or distractions) have been made and the symptoms of ADHD are still causing impairment, medication (first line: stimulants, followed by the non-stimulant atomoxetine) should be offered. [17]

The non-pharmacological treatment is considered for the ADHD adult groups who have made an informed choice not to have medication, have difficulty adhering to medication, and found medication to be ineffective or cannot tolerate it.[17] However, when non-pharmacological treatment is indicated for adults with ADHD, a structured supportive psychological intervention focused on ADHD and a regular follow-up should be offered.[17]

In adults with ADHD who have benefited from medication but whose symptoms are still causing significant impairment in at least one domain, the non-pharmacological treatment in combination with medication will be considered.[17]

EFFICACY AND SAFETY

Based on the systematic search up to 9th September 2024, there were 4 articles retrieved from the scientific databases (Ovid Medline, PubMed), and general search engines [Google Scholar]. There were two-phase 3, two-phase 2, a phase 1 and indirect comparison study of centanafadine with other drugs used in management of ADHD were retrieved. Only one phase 1 study were excluded while other study was included in this review.

Clinical effectiveness evidence of centanafadine is supported by the two phase 3 studies conducted evaluating its efficacy in adults with ADHD.[18] Both studies were randomised, double-blind, multicenter, placebo-controlled trials.[18] The studies consisted of four periods

which are screening and washout (up to 28 days), single-blind placebo run-in (1 week), double-blind treatment (6 weeks); and follow-up after the last dose of centanafadine (10 days) as shown in figure 2.[18]

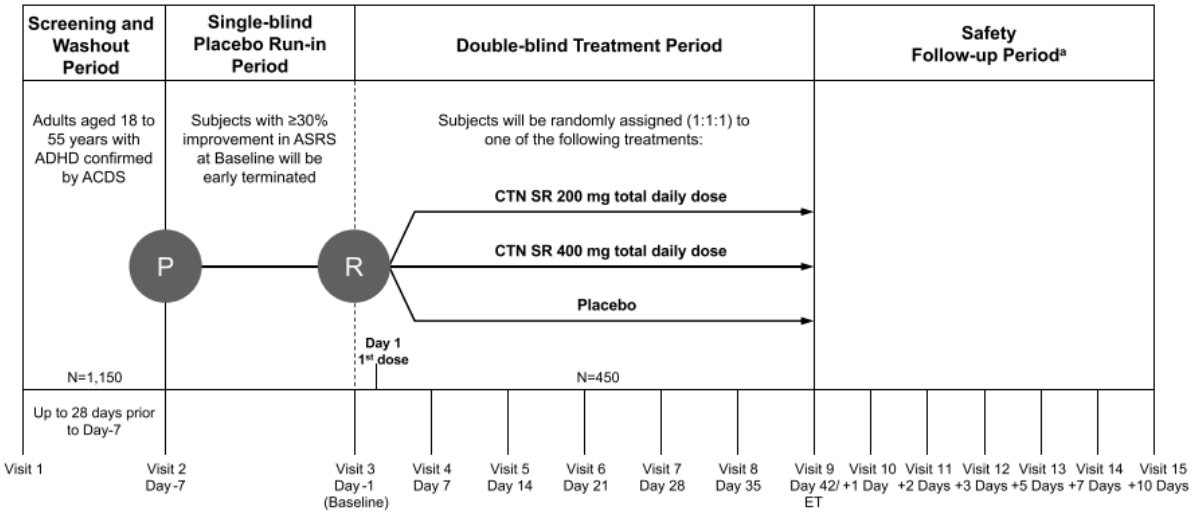

Figure 2: Study design schematic for study one and study two.[18]

The primary efficacy endpoint of both studies was the change from baseline at day 42 in the adult ADHD Investigator Symptom Rating Scale (AISRS) total score and the key secondary outcomes was changed from baseline at day 42 on the Clinical Global Impression–Severity of Illness Scale (CGI-S).[18] At day 42, statistically significant least-squares mean differences in AISRS total score were observed in favor of centanafadine versus placebo in study one (200 mg/d: −3.16, p= 0.019; 400 mg/d: −2.74, p= 0.039) and study 2 (200 mg/d: −4.01, p= 0.002; 400 mg/d: −4.47, p= 0.001).[18] Effect sizes versus placebo were −0.28 for 200 mg/d and −0.24 for 400 mg/d in study 1 and −0.37 for 200 mg/d and −0.40 for 400 mg/d in study 2.[18] In study one, the AISRS total scores at day 42 were reduced by 25.5% for subjects who were treated with centanafadine 200 mg/d, 24.6% for subjects who were treated with centanafadine 400mg/d, and 17.7% for subjects who received placebo.[18] In study two, the AISRS total scores at day 42 were reduced by 32.2% for subjects in the centanafadine 200 mg/d and the centanafadine 400 mg/d dose groups and 21.4% for subjects in the placebo group.[18] In study 2, statistically significant differences in AISRS scores were seen as soon as day 7 and were maintained to the end of treatment.[18] In both studies, centanafadine 200 and 400 mg/d achieved the key secondary endpoint of statistically significant improvements in CGI-S score versus placebo.[18] Overall, both studies showed statistically significant symptom improvement with centanafadine 200 and 400 mg/d compared with placebo in primary and secondary endpoints, AISRS total score, and CGI-S score, respectively.

The overall rate of treatment-emergent adverse events (TEAEs) in both of the phase 3 trials was low, but there was a small increase in TEAE occurrence with increasing dose.[18] Incidences of serious TEAEs and abuse potential–related AEs were low. The most common TEAEs reported by subjects who received centanafadine were headache and decreased appetite.[18] The most commonly reported TEAEs considered potentially related to the study medication increased slightly in frequency with increasing dose, were decreased appetite (5.1% for centanafadine 200 mg/d, 6.5% for centanafadine 400 mg/d, and 1.7% for placebo), headache (2.0% for centanafadine 200 mg/d, 4.5% for centanafadine 400 mg/d, and 2.4% for placebo), dry mouth (2.7% for centanafadine 200 mg/d, 5.5% for centanafadine 400 mg/d, and 0.3% for placebo), and nausea (1.7% for centanafadine 200 mg/d, 5.5% for centanafadine 400 mg/d, and 1.4% for placebo).[18] Overall, 36 subjects (4.1%) discontinued the study medication due to TEAEs: 14 subjects (4.8%) in the centanafadine 200 mg/d group, 18 subjects (6.2%) in the centanafadine 400 mg/d group, and 4 subjects (1.4%) in the placebo group.[18] These findings suggest that centanafadine has a favorable safety profile with manageable side effects.

Additionally, there were two phase 2 randomised controlled trials conducted previously to provide initial signals of the efficacy of centanafadine doses up to 500 mg/d and to further evaluate the efficacy and tolerability of centanafadine at the target dose.[19] It was a flexible-dose, single-blind, exploratory trial conducted in United States sites. The phase 2a study enrolled 37 male patients aged 18 and 55 years old, meanwhile, the phase 2b study enrolled 60 patients aged 18 to 60 years old.[19] The primary outcome of both studies was the mean total ADHD Rating Scale-IV (ADHD-RS-IV) score.[19] In the phase 2a study, mean ADHD-RS-IV total score decreased by 21.41 (standard deviation 10.74) from the start of active centanafadine treatment to the end of week 4 ($p<0.001$).[19] In the phase 2b study, centanafadine treatment resulted in a statistically significant improvement in ADHD-RS-IV from baseline to week 3 compared with placebo (least-squares mean −16.5 vs −8.4; $p<0.001$; effect size 0.66), with significant efficacy demonstrated as early as week 1.[19] This two phase 2 studies demonstrated that centanafadine 400 mg/d was effective, as assessed using the ADHD-RS-IV and well tolerated.

The latest update on the ongoing trials involving centanafadine was a phase 3, multicenter, open-label, long-term trial evaluating the long-term safety and tolerability of once-daily centanafadine capsules in children and adolescents with ADHD which started in February 2024.[20] This study is currently in recruiting stage with an estimated enrollment of 700 participants and expected to be completed by November 2024.[20]

In a matching-adjusted indirect comparison study of centanafadine versus lisdexamfetamine, methylphenidate and atomoxetine across matched population, centanafadine showed a significantly better short-term safety profile than lisdexamfetamine, atomoxetine, and viloxazine.[21] However, the efficacy was lower than with lisdexamfetamine and comparable with atomoxetine and viloxazine.[21] Considering its consistently favorable safety profile, centanafadine may represent a promising treatment option for adults with ADHD, particularly those with safety concerns, with the potential to address some of the unmet needs related to treatment-related adverse events.[21]

ESTIMATED COST

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

POTENTIAL IMPACT

In summary, early evidence showed centanafadine improves symptoms associated with ADHD in adults and it has the potential to address several unmet requirements related to treatment-associated adverse events given its consistently favourable safety profile.

However, further research is needed to determine the clinical efficacy, safety, and cost implication of centanafadine in comparison to the current treatment over extended periods of use.

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