KEY FINDINGS

Intervention	Comparators	Evidence Rating	US Price	Health-Benefit Price Benchmark (HBPB)
Early Parkinson's Disease				
Tavapadon	No additional pharmacologic treatment	C++ : moderate certainty of a small to substantial net health benefit	$58,800	Not calculated for this population
	Levodopa	P/I: promising, but inconclusive		
	Dopamine Agonists	P/I: promising, but inconclusive		
	MAO-B inhibitors	P/I: promising, but inconclusive		
Parkinson's Disease with Motor Fluctuations				
Tavapadon plus Levodopa	Levodopa alone	C++ : moderate certainty of a small to substantial net health benefit	$58,800	$4,800 to $6,900 per year
	Dopamine Agonists plus levodopa	P/I: promising, but inconclusive		
	COMT inhibitors plus levodopa	P/I: promising, but inconclusive		
	MAO-B inhibitors plus levodopa	P/I: promising, but inconclusive		

"Tavapadon provides a net health benefit over no additional pharmacological treatment, but there are open questions about its benefits compare to other available symptomatic treatments. Unfortunately, the manufacturer chose a price for tavapadon far above any reasonable estimate of a value-based price. This may lead payers to implement formulary restrictions to limit provider and patient access to this new treatment."

– ICER's Chief Scientific Officer and Director of Health Technology Assessment Methods and Engagement, Dan Ollendorf, PhD, MPH

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THEMES AND RECOMMENDATIONS

- Payers could reasonably limit coverage to patients whose clinical characteristics are consistent with those studied in the pivotal clinical trials.
- For patients with early Parkinson's disease, manufacturers and research funders should support head-to-head trials of tavapadon compared with levodopa. Similarly, for patients with Parkinson's disease receiving levodopa who experience motor fluctuations, manufacturers and research funders should support head-to-head trials of tavapadon compared with other once-daily dopamine agonists.
- Clinical research should give greater attention to the non-motor manifestations of Parkinson's disease, including cognitive function, and to therapies that improve these outcomes.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by stiffness, slowed movement, tremor, instability, and a range of non-motor symptoms, including difficulties with thinking, depression, anxiety, and insomnia. In the United States (US), approximately 1.2 million individuals are estimated to be living with PD or atypical Parkinsonism, with prevalence projected to increase significantly as the population ages.

Patients described PD as a progressive condition characterized by a prolonged and often frustrating diagnostic journey, increasing functional impairment, and the need for continuous adjustment of therapy. The greatest burdens were the loss of motor function and the unpredictability of symptom control. Patients emphasized that relatively small changes in motor ability can substantially affect independence and quality of life. Difficulties performing routine tasks, such as tying shoes or walking safely, were highlighted as meaningful indicators of disease progression and treatment benefit.

Levodopa remains the most effective symptomatic therapy for motor symptoms. However, long-term treatment is frequently associated with motor fluctuations and dyskinesias (involuntary muscle movements), and patients typically need to take pills three to five times a day to manage their symptoms. Dopamine agonists (e.g., pramipexole, ropinirole, rotigotine) are used as initial therapy in selected patients or as adjunctive therapy to levodopa in patients with motor fluctuations, but are associated with adverse effects, including sleepiness, low blood pressure when standing up, hallucinations, and impulse control disorders (e.g., pathological gambling, hypersexuality, compulsive buying or eating, etc.). Additional adjunctive options include monoamine oxidase-B (MAO-B) inhibitors, which block the enzyme that breaks down dopamine and catechol-O-methyltransferase (COMT) inhibitors, which block the enzyme that breaks down levodopa.

Tavapadon (JUVMO™, AbbVie Inc.) is an oral, once-daily, selective dopamine D1/D5 partial agonist recently approved by the Food and Drug Administration (FDA) for for the treatment of Parkinson's disease in adults. Unlike currently

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Clinical Analyses

available dopamine agonists, which primarily target D2/D3 receptors, tavapadon selectively targets D1-like receptors. The side effects that limit the use of dopamine agonists (sleepiness, low blood pressure when standing up, hallucinations, and impulse control disorders [ICD]) are thought to be due to D2 and D3 receptor effects.

The greatest uncertainties arise because we lack head-to-head trials between tavapadon and other drugs, particularly versus levodopa alone and the combination of levodopa plus a dopamine agonist. Hence, our assessment of comparative effectiveness relies on indirect comparisons. Additional uncertainties are due to the relatively short follow-up time of the studies of tavapadon. For example, impulse control disorder symptoms matter a lot to patients and their care partners. Observational studies suggest that the incidence of these symptoms increases steadily over several years. The relatively short follow-up time of the pivotal TEMPO trials could mask either a greater incidence over time or a flattening of the incidence curve that would demonstrate greater benefits of tavapadon compared with the older medications.

As expected, tavapadon significantly improved scores on the UPDRS Parts II and III compared with no additional treatment among patients with early PD. However, quality-of-life measures improved only minimally. There were some patients with ICDs and hallucinations in the tavapadon group and none in the placebo group. In addition, the discontinuation rate due to adverse events (AEs) was much higher in the tavapadon group. Given the mix of benefits and harms and the lack of follow-up beyond six months for the primary outcomes, the comparative net health benefit compared with no additional pharmacologic treatment is comparable or better (C++).

The evidence comparing tavapadon with other comparators (levodopa, dopamine agonists, MAO-B inhibitors) as monotherapies is less clear. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. In the network meta-analyses (NMAs), the evidence for the benefits of tavapadon on the UPDRS is mixed. There are no clear benefits in quality of life, and the within-trial discontinuation rates due to AEs were higher for tavapadon. Given the mixed results and low certainty of evidence, the net health benefit is promising, but inconclusive (P/I) for all three comparisons.

As expected, tavapadon significantly reduced OFF time compared with placebo in patients on levodopa who are experiencing motor fluctuations. However, there were no significant improvements in quality of life. The overall discontinuation rate was significantly higher in the tavapadon group. Given the mix of benefits and harms and the lack of follow-up beyond six months for the primary outcomes, the comparative net health benefit compared to levodopa alone is comparable or better (C++).

The evidence comparing tavapadon with the other therapies (dopamine agonists, MAO-B inhibitors, COMT inhibitors) as an adjunct therapy to levodopa is less clear. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. Within-trial discontinuation rates due to AEs were significantly higher for tavapadon compared with each of the comparators. Given the lack of significant benefits, evidence of more discontinuations and low certainty, the net health benefit is promising, but inconclusive (P/I) for all three comparisons.

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Economic Analyses

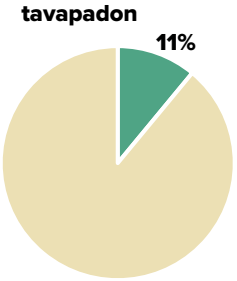
LONG-TERM COST EFFECTIVENESS

Using two semi-Markov models built with real-world Parkinson's disease data (Parkinson's Precision Medicine Initiative, Michael J Fox Foundation) and treatment effects from the TEMPO trials as well as the network meta-analyses (NMA), we estimated the cost-effectiveness of tavapadon for early Parkinson's disease (versus levodopa alone) and as an adjunct to levodopa for Parkinson's disease with motor fluctuations (versus other dopamine agonists added to levodopa). At a wholesale acquisition cost (WAC) of $58,800 per year, tavapadon was more costly and slightly less effective versus levodopa in early PD. The estimated cost-effectiveness for tavapadon compared with a market basket of dopamine agonists in patients already on levodopa was approximately $10 million per equal value life year (evLY) gained as well as per quality adjusted life year (QALY), based on a small estimate of overall benefit driven primarily by reductions in the rate of ICDs. These results were consistent under the health care sector and modified societal perspectives but varied substantially in sensitivity analyses, especially for the early PD population. The results were most sensitive to the estimates of the magnitude and durability of tavapadon benefits. These estimates should be interpreted considering the uncertainties in the model, as small changes in effectiveness estimates could markedly affect results.

POTENTIAL BUDGET IMPACT

At the current price of tavapadon (list price of $58,800 per year), 11% of the eligible population could be treated before reaching the ICER potential budget impact threshold of $821 million. Therefore, ICER is issuing an access and affordability alert for tavapadon.

The purpose of an ICER access and affordability alert is to signal to stakeholders and policymakers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.



Percent of eligible Parkinson's disease patients that could be treated in a given year before crossing the ICER potential budget impact threshold.

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Public Meeting Deliberations

VOTING RESULTS

ICER assessed, and the independent appraisal committee voted, on the evidence for the net health benefit of tavapadon.

ICER's Public Meeting: Voting Results on Clinical Effectiveness and Benefits Beyond Health

- The panelists unanimously found (13-0) that current evidence is **adequate** to demonstrate a net health benefit for tavapadon when compared to no additional pharmacological treatment (for patients with early Parkinson's disease).
- A majority found (12-1) that current evidence is **not adequate** to demonstrate a net health benefit for tavapadon when compared to levodopa, dopamine agonists (DAs), or monoamine oxidase-B (MAO-B) inhibitors (for patients with early Parkinson's disease).
- A majority found (9-4) that current evidence is **adequate** to demonstrate a net health benefit for tavapadon plus levodopa when compared to levodopa alone (for patients on levodopa – and possibly on stable doses of other therapies – experiencing motor fluctuations).
- A majority found (12-1) that current evidence is **not adequate** to demonstrate a net health benefit for tavapadon plus levodopa when compared to of DAs plus levodopa, MAO-B inhibitors plus levodopa, or catechol-O-methyltransferase (COMT) inhibitors plus levodopa (for patients on levodopa – and possibly on stable doses of other therapies – experiencing motor fluctuations).

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and weighed special ethical obligations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- If payment/cost were not issues, tavapadon is likely to provide **a small improvement** to access to treatment because of its method of delivery and/or treatment setting.

ICER's Public Meeting: Voting Results on Long-Term Value for Money

ICER has calculated a health benefit price benchmark (HBPB) for tavapadon to be between $4,800 and $6,900 per year for Parkinson's disease with motor fluctuations. AbbVie's list price for tavapadon is $58,800 per year. A discount of 88 to 92% would be needed from the list price to reach ICER's fair price range.

For early Parkinson's disease, ICER could not calculate a health benefit price benchmark (HBPB) due to significant uncertainty regarding the mix of benefits and harms.

After reviewing the clinical evidence and considering the treatments' benefits beyond health noted above, the CTAF evaluated the long-term value of tavapadon:

- For patients with early Parkinson's disease, the panelists unanimously found (13-0) found that at current pricing, tavapadon represents **"low"** long-term value for money.
- For patients with Parkinson's disease with motor fluctuations, the panelists unanimously found (13-0) found that at current pricing, tavapadon plus levodopa compared to DAs plus levodopa represents **"low"** long-term value for money.

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.

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