Tavapadon for Parkinson's Disease

Draft Background and Scope

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Background

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.[1] PD is more common in non-Hispanic whites, though this may reflect underdiagnosis in populations with less access to care. It also occurs more commonly in men than in women.[1] The estimated global prevalence of PD has more than doubled over the past two decades.[2] In the United States, approximately one million individuals are estimated to be living with PD, with prevalence projected to increase significantly as the population ages.[3]

Levodopa remains the most effective symptomatic therapy for motor symptoms.[1] However, long-term treatment is frequently associated with motor fluctuations and dyskinesias. 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. Additional adjunctive options include monoamine oxidase-B (MAO-B) inhibitors which block the enzyme that breaks down dopamine, catechol-O-methyltransferase (COMT) inhibitors which block the enzyme that breaks down levodopa, istradefylline which reduces gamma-aminobutyric acid (GABA) inhibition, and amantadine formulations which increase dopamine release and decrease dopamine reuptake.[1]

PD is associated with substantial economic burden. Total annual US costs have been estimated at $52 billion in 2017, about equally split between direct medical costs and indirect costs related to lost productivity and informal caregiving.[3] Costs increase with disease progression and the development of motor complications, cognitive impairment, and institutional care needs.

Tavapadon (AbbVie Inc.) is an oral, once-daily, selective dopamine D1/D5 partial agonist under review by the Food and Drug Administration (FDA) for use as monotherapy in early PD and as adjunctive therapy in patients experiencing motor fluctuations.[4] Unlike currently 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) are thought to be due to D2 and D3 receptor effects. Tavapadon may avoid these important concerns.

Stakeholder Input

ICER engaged with patient advocacy organizations, clinical experts, and the manufacturer to better understand the treatment landscape for PD, unmet needs, and the potential role of tavapadon. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Representatives from patient advocacy organizations emphasized that PD affects both motor and non-motor functioning and that symptom burden varies substantially across individuals.

Motor symptoms—particularly bradykinesia, rigidity, tremor, and gait impairment—remain central to diagnosis and treatment decisions. However, stakeholders stressed that non-motor symptoms such as fatigue, depression, cognitive changes, hallucinations, and sleep disturbance are often underrecognized and may have equal or greater impact on quality of life.

A consistent theme was the unpredictability of motor fluctuations and medication response. Patients value consistent "ON" time and report that wearing-off periods significantly disrupt daily functioning. Complex dosing regimens, particularly with levodopa, were described as burdensome and may affect adherence. Once-daily therapies were viewed as potentially reducing treatment burden.

Stakeholders also highlighted the substantial burden on caregivers, particularly when cognitive or behavioral symptoms emerge, the likelihood of falls as PD progresses, representing a major driver of cost and caregiver strain, and barriers to care among underinsured populations.

Clinical experts generally reported that levodopa remains the most effective and commonly used first-line therapy, particularly for patients aged 60 years and older. Dopamine agonists and MAO-B inhibitors are used less frequently as initial therapy due to more modest efficacy or concerns about adverse effects.

Neuropsychiatric adverse events associated with dopamine agonists—including impulse control disorders, hallucinations, somnolence, and orthostatic hypotension—were identified as important limitations of current options. Several clinicians indicated that a similar therapy with a more favorable side effect profile could address an unmet need.

Motor fluctuations and dyskinesias were described as major drivers of treatment adjustments and consideration of advanced therapies such as deep brain stimulation (DBS) or infusion pumps. Cognitive impairment was viewed as a key factor limiting eligibility for surgical intervention.

Several experts expressed interest in tavapadon as an additional option, particularly if it demonstrates improved tolerability relative to existing dopamine agonists and can be used both as monotherapy and adjunctive therapy.

The manufacturer, AbbVie Inc., indicated that tavapadon is being developed for use in early PD and as adjunctive therapy in patients with motor fluctuations. Comparators suggested include levodopa/carbidopa, dopamine agonists, MAO-B inhibitors, and other adjunctive agents.

The manufacturer emphasized the importance of evaluating adverse events, including impulse control disorders, ON and OFF time, patient-reported outcomes, and caregiver and societal impact measures.

Report Aim

This project will evaluate the health and economic outcomes of tavapadon for Parkinson's disease. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider the combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction,

and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The populations for this are:

- Population 1: Adults with early-stage PD (defined as modified Hoehn and Yahr stages 1-2)
- Population 2: Adults with PD and on levodopa who are experiencing motor fluctuations

Data permitting, we will evaluate the evidence for treatment effect modification by subgroups defined by age (e.g., <60 years, ≥60 years) and sex at birth.

Intervention

- Population 1: Tavapadon
- Population 2: Tavapadon plus levodopa

Comparators

- Population 1: Levodopa
- Population 2: Dopamine agonists (pramipexole extended-release [ER], ropinirole ER, and rotigotine transdermal patch) plus levodopa

Based on discussions with clinical experts and the different mechanisms of action, we focused our attention on comparators with similar mechanisms to tavapadon and thus decided to exclude other drug classes that are commonly used as adjuncts to levodopa to manage motor fluctuations (MAO-B inhibitors, COMT inhibitors).

Outcomes

Patient-Important Outcomes

- Changes from baseline in MDS-UPDRS Parts II and III scores (individual and combined scores)
- Changes from baseline in Hauser Diary motor state durations
    - OFF time
    - ON time without troublesome dyskinesia
    - ON time with troublesome dyskinesia
- Health-related quality of life measures
    - Parkinson's Disease Questionnaire (e.g., PDQ-8, PDQ-39)
    - EQ-5D
    - SF-36
- Activities of daily living
- Caregiver burden
- Adverse events including
    - Serious drug-related adverse events
    - Impulse control disorders (ICD)
    - Dyskinesia
    - Orthostatic hypotension
    - Insomnia
    - Sleep disorder
    - Falls

Other Outcomes

- Discontinuations due to adverse events
- Other disability measures (e.g., self-assessment Parkinson's disease disability scale [SPDDS])
- Fatigue
- Pain
- Cognitive assessments
- Constipation

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on June 3, 2026. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments, consistent with the clinical evidence review. The model structure will be based in part on a literature review of prior published models of PD. Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity, interactions with the criminal justice system) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness

ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement an "indirect" method to capture the potential impacts of tavapadon on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).[5]

The target population will consist of individuals with PD, including both early stage (i.e., when monotherapy with tavapadon may be considered) and advanced stage (when tavapadon may be used as an adjunct to levodopa) patients. The modeling framework may evaluate these groups within a single cohort or as separate cohorts, depending on the analytic objectives and data availability.

The model structure may include health states defined according to disease severity and motor symptom progression. Health states can be based on disease severity scales such as Hoehn and Yahr (H&Y) stage, motor fluctuation measures including ON and OFF time, or categorical classifications such as Mild, Moderate, and Severe defined by Unified Parkinson Disease Rating Scale (UPDRS) scores. A combined approach incorporating both severity staging and ON and OFF time measures may also be applied.

Disease progression may be captured using changes in UPDRS components, including Part II and Part III together or Part III alone, depending on the availability of clinical data and relevance to the modeled outcomes.

A cohort of patients will transition between states during predetermined cycles (of three-months) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using clinical trial data and network meta-analysis, if available.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of major PD-related clinical events avoided as data allow (e.g., duration of OFF/ON time) , life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years (evLYs) gained. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons

will be made between tavapadon and its comparators, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per major PD-related clinical events avoided (including falls, fractures, and institutionalization).

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by use of tavapadon (e.g., management of adverse events), as these services (see below) will not be captured in the economic model. Rather, we are seeking services used in the current management of Parkinson's Disease beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

For example, the following have been suggested as low-value services related to Parkinson's disease in a Choosing Wisely publication.[6]

1. Do not use the brain single photon emission tomography with tracers for dopaminergic transporters (DAT-SPECT) for the prognosis and to ascertain the progression of Parkinson's disease.

2. Do not use antipsychotic medication except clozapine and quetiapine to treat psychosis in Parkinson's disease.

3. Do not use myocardial scintigraphy with metaiodobenzylguanidine (MIBG) to diagnose Parkinson's disease.

4. Do not use anticholinergic drugs to treat the motor symptoms of drug-induced parkinsonisms.

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