Aldosterone Synthase Inhibitors for the Treatment of Hypertension

Draft Background and Scope

MARCH 30, 2026

Background

Hypertension is a very common, chronic condition, defined clinically by a blood pressure consistently greater than 130/80 mmHg (millimeters of mercury). It affects nearly half of US adults, with higher rates in men and non-Hispanic African Americans.[1] Almost 20% of adults are not aware of their diagnosis.[2] The causes of hypertension are multifactorial, including genetics, environmental (e.g., air pollution), dietary influences (e.g., high sodium intake, alcohol), and psychosocial stressors.[3] Although hypertension often does not cause symptoms, over time, the elevated pressure can damage arteries, resulting in a higher risk for heart attacks, strokes, chronic kidney disease, dementia, and heart failure.[4] It is a contributing factor to over 600,000 deaths in the United States each year.[5] Medical costs resulting from hypertension in the US are estimated to be upwards of $219 billion annually.[6]

Treatment of hypertension involves both lifestyle changes and medications. Diet modifications, such as the Dietary Approaches to Stop Hypertension (DASH) diet, are recommended by clinical practice guidelines, along with weight loss (if overweight or obese), increased physical activity, and stress reduction.[3] If blood pressure is not controlled to a goal of less than 130/80 mmHg with lifestyle and psychosocial measures, clinical practice guidelines recommend adding medication for many of these patients.[3] First-line antihypertensive therapies include thiazide-type diuretics, dihydropyridine calcium channel blockers (CCB), and angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) and can be used as monotherapy or combination therapy. While blood pressure lowering has been associated with a reduction in cardiovascular events and all-cause mortality, there is inconsistent evidence on the strength of this association with this surrogate marker.[7]

Despite effective treatments, more than 75% of adults with hypertension still have uncontrolled blood pressure (blood pressure ≥130/80 mmHg), with African American, Hispanic, and Asian adults more likely to have uncontrolled hypertension compared to White adults.[1,8] There are many reasons for this: one survey of US adults showed that 31% were non-adherent to medications;[9] clinical inertia by physicians, difficulty accessing healthcare, lack of insurance, and having an underlying medical cause (secondary hypertension) are other common causes of uncontrolled

hypertension.[10,11] Resistant hypertension is defined as a blood pressure of ≥130/80 mmHg while a person is on three or more antihypertensives (ACEi/ARB + CCB + thiazide diuretic) at maximally tolerated doses or a blood pressure of <130/80 mmHg but requires four or more antihypertensives.[3] For patients with resistant hypertension that is uncontrolled, the addition of a mineralocorticoid receptor antagonist (MRA) such as spironolactone or eplerenone is recommended.[3] However, use of spironolactone is often limited by side effects such as gynecomastia and high potassium levels. While there are alternative antihypertensives, such as amiloride, if a person does not tolerate an MRA,[12] there are limited data to guide the choice of a fifth line agent.

A new class of medications called aldosterone synthase inhibitors (ASI) has been developed to treat hypertension. Two ASI drugs, baxdrostat (AstraZeneca) and lorundrostat (Mineralys Therapeutics), are under consideration for approval by the US Food and Drug Administration for the treatment of hypertension.[13,14] Unlike MRAs, which block the aldosterone receptor, ASI therapies decrease production of aldosterone. Aldosterone levels appear to be higher in patients with resistant hypertension,[15] and by decreasing production of aldosterone, ASI drugs may decrease blood pressure. Baxdrostat has a PDUFA date in the second quarter of 2026, while lorundrostat has a PDUFA date of December 22, 2026.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with some stakeholders (clinicians and manufacturers) and publicly available patient stories, as we have not yet spoken directly with patients or patient groups. 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.

Although hypertension can result in end-organ damage such as strokes, heart attacks, or end-stage kidney disease, many persons living with hypertension do not have symptoms directly attributable to high blood pressure. Consequently, some persons with hypertension do not become aware of their condition until they have either severe hypertension (blood pressure higher than 180/110 mmHg) or they have an event such as a heart attack or stroke. Some persons with hypertension report stress playing a large role in their lives prior to diagnosis, and also not being aware of how diet, particularly salt intake, may impact their health.[16]

After diagnosis, persons living with hypertension report focusing on lifestyle modifications such as decreasing stress, decreasing salt in the diet, and increasing physical exercise.[16] Some persons living with hypertension report struggling with medication adherence, including remembering to take medications daily, particularly if taking multiple medications, and managing side effects.[16]

Clinical experts emphasized that single pill combinations can help increase adherence to medications, but that some patients remain uncontrolled or have resistant hypertension even when they are taking medications regularly. For such patients, mineralocorticoid receptor antagonists such as spironolactone are the preferred option; however, spironolactone may be difficult to take due to side effects, particularly for men. We also heard that there is clinical inertia when managing blood pressure and that it often takes three to six months to adjust or add a blood pressure medication, even in people with uncontrolled hypertension.

Report Aim

This project will evaluate the health and economic outcomes of baxdrostat and lorundrostat for the treatment of uncontrolled or resistant hypertension. 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 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

We have identified two populations of interest:

- Adults with uncontrolled hypertension despite use of two antihypertensive agents and who do not tolerate a third antihypertensive agent recommended by clinical guidelines.
- Adults with uncontrolled resistant hypertension, not on spironolactone or eplerenone.

Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors including age, sex, and race/ethnicity
- Baseline systolic blood pressure, body mass index, and kidney function (estimated glomerular filtration rate)

Interventions

The full list of interventions is as follows:

- Baxdrostat
- Lorundrostat

Comparators

Data permitting, we intend to compare the agents to each other and to:

- Mineralocorticoid receptor antagonists
    - spironolactone
    - eplerenone
- Amiloride

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Cardiovascular events (e.g., stroke, ischemic heart disease, incident heart failure)
    - Renal events (e.g., end-stage renal disease)
    - Mortality
    - Cognitive outcomes (e.g., dementia, Alzheimer's)

    - Quality of life
    - Adverse events including:
        - Gynecomastia
        - Erectile dysfunction
        - Serious adverse events
- Other Outcomes
    - Reduction in blood pressure
    - Asymptomatic chronic kidney disease
    - Other adverse events including:
        - Asymptomatic chronic kidney disease
        - Hyponatremia (low sodium)
        - Hyperkalemia (elevated potassium)

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least four weeks 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 23, 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 baxdrostat and lorundrostat compared to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of uncontrolled or resistant hypertension. 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 a method to capture the potential impacts of baxdrostat and lorundrostat on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

Two target populations will be modeled. Mirroring the clinical evidence review, the first will consist of adults with uncontrolled hypertension despite use of two hypertensive agents and who do not tolerate a third agent recommended by clinical guidelines. The second will consist of adults with resistant hypertension, defined as blood pressure that remains above goal despite concurrent use of three agents of different classes. The model is expected to include health states related to uncontrolled or resistant hypertension, and health states reflecting potential downstream consequences of hypertension, such as cardiovascular events (e.g. coronary heart disease, stroke, myocardial infarction, and heart failure) and renal events (e.g. end stage renal disease). A cohort of patients will transition between states during predetermined cycles (potentially three-month cycles in the first year to align with clinical trial results followed by annual cycles) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will 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, literature, and data permitting, internal analyses such as a network meta-analysis.

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 cases of coronary heart disease, stroke, myocardial infarction, heart failure, and end-stage kidney disease avoided in addition to life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLY). 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 treatments, 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 coronary heart disease, stroke, heart failure, and end-stage kidney disease avoided.

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 baxdrostat and lorundrostat (e.g., reduced need for emergency care for hyperkalemia), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of hypertension 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.

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