INDEPENDENT EVIDENCE SYNTHESIS

Imeglimin

Pharmacology, mitochondrial mechanisms, clinical efficacy, safety, renal dosing and longevity assessment

Evidence reviewed through 27 August 2026

0.6-0.9%	2,000 mg/day	No evidence
Typical placebo-adjusted HbA1c reduction	Standard Japanese total daily dose	For cardiovascular outcomes or lifespan extension

A detailed review of the first-in-class glimin for type 2 diabetes, separating demonstrated human effects from preclinical mitochondrial hypotheses and unsupported longevity claims.

Contents

This is an evidence review, not a recommendation to obtain or take imeglimin. It is a prescription medicine for type 2 diabetes in the countries where it is authorised. Its suitability depends particularly on kidney function, concurrent glucose-lowering medicines, gastrointestinal tolerance, pregnancy status, acute illness and the treatment goal.

Executive assessment

Imeglimin hydrochloride (brand **Twymeeg** in Japan) is a first-in-class oral glucose-lowering drug in the tetrahydrotriazine or “glimin” class. It is chemically related to metformin but is not simply a newer metformin. Its best-supported pharmacology is a combination of:

1. glucose-dependent amplification of pancreatic beta-cell insulin secretion;
2. reduced hepatic glucose production;
3. improved insulin-mediated glucose disposal; and
4. modulation of mitochondrial redox biology, including suppression of reverse-electron-transport-derived reactive oxygen species in some experimental systems.

The pivotal Japanese placebo-controlled trial found a **0.87 percentage-point placebo-adjusted reduction in HbA1c over 24 weeks** at 1,000 mg twice daily. Across trials, the usual effect is moderate-roughly comparable to several established oral agents-while body weight and blood pressure are generally neutral. Hypoglycaemia risk is low when imeglimin is used alone, but rises when it is combined with insulin, sulfonylureas or glinides. Gastrointestinal effects are the main tolerability problem, particularly at higher doses and with metformin.

The major evidence deficit is clinical outcomes. There is still **no published cardiovascular-outcome trial, kidney-outcome trial, mortality trial or human ageing/longevity trial**. Consequently, imeglimin has not shown that it prevents myocardial infarction, stroke, heart failure, kidney failure or death. Its mitochondrial, beta-cell, vascular and organ-protective findings are mechanistically interesting but mostly preclinical.

The most defensible overall verdict is:

- **For lowering glucose in type 2 diabetes:** effective, with moderate-quality evidence and a generally manageable safety profile.
- **As a replacement for metformin:** not proven superior; it may be useful when metformin is insufficient or poorly tolerated, but comparative evidence is sparse.
- **For cardiovascular or renal protection:** unproven.
- **For longevity or use by metabolically healthy people:** speculative and unsupported.

1. Identity, chemistry and regulatory status

Property	Detail
Generic name	Imeglimin; marketed as the hydrochloride salt
Brand	Twymeeg in Japan; multiple brands/generics in India
Class	Tetrahydrotriazine; first marketed “glimin”
Free-base formula	C6H13N5; molecular mass about 155.2 g/mol
Hydrochloride formula	C6H14ClN5; molecular mass about 191.66 g/mol
Japanese dosage form	500 mg immediate-release tablet
Approved indication	Type 2 diabetes mellitus-not type 1 diabetes, prediabetes, obesity or ageing

Japan approved imeglimin in June 2021 and launched Twymeeg in September 2021. It remains marketed there by Sumitomo Pharma. India’s regulator listed 500 mg and 1,000 mg tablets for type 2 diabetes in October 2022, and subsequent-release formulations have also been authorised. As of the report date, imeglimin is **not an FDA-, EMA- or MHRA-authorised medicine** and has no NHS product or UK prescribing pathway. A substance entry in an FDA chemistry database is not a marketing approval. Poxel current status, CDSCO 2022 approvals, PMDA product page

The standard Japanese adult dose is **1,000 mg twice daily**, morning and evening. A 1,500 mg twice-daily dose produced little additional HbA1c reduction but substantially more gastrointestinal intolerance, which is why 1,000 mg twice daily was selected for phase 3 and marketing. Food delays and modestly lowers the peak concentration but has no clinically important effect on overall exposure. Current Japanese label, phase 2b dose-ranging trial

2. Pharmacokinetics

Absorption and exposure

Imeglimin is absorbed fairly rapidly, with a typical time to peak plasma concentration of about 2-4 hours. At repeated dosing, steady state is reached in about five days. Reported terminal half-lives vary with the sampling design but are commonly around 10-14 hours, consistent with twice-daily administration. Exposure becomes less than dose-proportional at high doses, suggesting saturable absorption.

After 1,000 mg twice daily in healthy volunteers, a reported steady-state peak concentration was approximately 1.8 micrograms/mL-roughly 10-12 micromolar as the hydrochloride. This concentration is worth remembering: several cell experiments that establish possible mitochondrial mechanisms use hundreds of micromolar to millimolar concentrations, so not every in-vitro observation can be assumed to occur in patients.

Distribution, metabolism and elimination

- Plasma protein binding is very low: approximately 1.2%-6.4%.
- Imeglimin undergoes little metabolism and has no important active metabolite.
- In a radiolabel mass-balance study, about 42% of the dose was recovered unchanged in urine and about 55% of radioactivity in faeces.
- It is a substrate of the organic-cation transporters OCT1/OCT2 and MATE1/MATE2-K. Renal filtration and active tubular secretion therefore contribute materially to elimination.
- It did not meaningfully inhibit or induce the principal CYP enzymes in vitro, so classic CYP-mediated interactions are unlikely.

These properties make kidney function more important than hepatic metabolism for dosing. The current label and detailed pharmacokinetic values are available in the Japanese prescribing information; early ethnic and dose-ranging pharmacokinetics are reported here.

3. Mechanism of action

3.1 The high-level model

Imeglimin addresses two broad abnormalities in type 2 diabetes:

- **Pancreatic:** it amplifies glucose-stimulated insulin secretion and appears to protect stressed beta cells in disease models.
- **Extra-pancreatic:** it reduces hepatic glucose output and improves insulin-mediated glucose disposal, particularly in skeletal muscle.

The word glucose-stimulated matters. Imeglimin has little insulin-secretory effect at low glucose in isolated-islet experiments, which helps explain its low intrinsic hypoglycaemia risk. This is not absolute protection: combination with other glucose-lowering drugs can still cause hypoglycaemia.

3.2 Beta-cell NAD+, calcium and insulin secretion

In diabetic rodent islets, imeglimin acutely increases the cellular NAD+ pool, apparently by increasing nicotinamide phosphoribosyltransferase-dependent NAD+ salvage. NAD+-derived signalling molecules, including cyclic ADP-ribose, promote intracellular calcium release through ryanodine-receptor/TRP-channel pathways. Together with improved glucose-stimulated ATP generation, this amplifies the calcium signal that triggers insulin-granule exocytosis.

Longer-term animal and cell studies report:

- improved beta-cell mitochondrial structure and ATP production;
- recovery of insulin granules;
- reduced oxidative stress and apoptosis;
- preserved beta-cell mass; and
- normalisation of excessive mitophagy in diabetic mouse beta cells.

This is a coherent mechanistic package, but preservation of human beta-cell mass has not been demonstrated directly. The key primary studies are the NAD+/glucose-stimulated insulin-secretion study and a 2024 diabetic-mouse mitophagy study.

3.3 Liver

Imeglimin suppresses gluconeogenesis in hepatocytes and diabetic animals. Proposed proximal events include a mild constraint on respiratory-chain flux, a fall in the hepatocyte ATP/ADP ratio and activation of AMPK. Unlike a poison such as rotenone, the relevant experimental work did not show loss of the maximum catalytic capacity of isolated Complex I. A later hepatocyte study also found reduced ATP-linked oxygen consumption and AMPK activation, but imeglimin was less potent than metformin and much of the work used concentrations well above normal human plasma exposure. Primary liver study, 2023 hepatocyte study

3.4 Skeletal muscle and insulin sensitivity

Preclinical studies and small human physiology studies suggest increased insulin-stimulated glucose uptake, improved Akt signalling and enhanced peripheral insulin sensitivity. These effects appear real enough to contribute to glucose lowering, but clinical evidence suggests that amplification of insulin secretion is at least as important and possibly dominant in many patients.

3.5 What does imeglimin actually do to mitochondrial Complex I?

This is the most frequently oversimplified part of the drug's pharmacology.

Claim	Evidence-based interpretation
"Imeglimin is a Complex I inhibitor."	Partly true in some functional assays, but too crude. It can constrain respiratory-chain electron flux under certain conditions.
"It directly blocks Complex I like rotenone."	Not supported. In isolated enzyme and endothelial-cell work it did not suppress forward, rotenone-sensitive Complex I catalytic activity in the classical fashion.
"It improves mitochondria."	Supported in several diabetic/stressed cell and animal models, but this is context-dependent and does not establish a universal enhancement of mitochondrial output.
"It reduces mitochondrial ROS."	Well supported preclinically, especially for ROS generated by reverse electron transport through Complex I.
"It proves mitochondrial protection in humans."	No. Human trials establish glucose lowering, not direct mitochondrial clinical benefit or organ protection.

In human endothelial cells, imeglimin selectively reduced reactive oxygen species produced by **reverse electron transport (RET)** through Complex I, delayed opening of the mitochondrial permeability-transition pore, and reduced cytochrome-c release and cell death. It did not suppress forward Complex I activity or basal oxygen consumption in that system. The best synthesis is therefore that imeglimin **modulates respiratory-chain flux and the redox state around Complex I**, suppressing pathological RET-derived ROS in some settings, rather than acting as a simple high-affinity Complex I poison. RET/mPTP primary study

3.6 Evidence hierarchy for the mechanism

Mechanistic proposition	Evidence level	Confidence
Lowers HbA1c and fasting glucose	Multiple randomised human trials	High
Amplifies glucose-dependent insulin secretion	Human biomarkers plus islet/animal work	Moderate-high
Improves peripheral insulin sensitivity	Small human physiology and preclinical work	Moderate
Suppresses hepatic gluconeogenesis	Predominantly preclinical	Moderate
Raises beta-cell NAD+ via salvage signalling	Isolated islets/animals	Moderate for mechanism; low for human clinical importance
Suppresses RET-derived Complex I ROS and mPTP opening	Cell/animal models	Moderate preclinically; low clinically
Preserves human beta-cell mass or prevents diabetes progression	Not demonstrated	Very low
Protects heart, kidney or brain in patients	No outcome trial	Very low
Extends lifespan	No relevant evidence	None

An integrated pharmacology review, including original sponsor-generated experiments, is available here.

4. Clinical efficacy in type 2 diabetes

4.1 Principal controlled and long-term trials

Study	Design and population	Main glycaemic result	Important limitation
Japanese phase 2b	299 patients; placebo vs 500, 1,000 or 1,500 mg twice daily; 24 weeks	Placebo-adjusted HbA1c: -0.52%, -0.94% and -1.00%, respectively	Dose-response flattened above 1,000 mg; more GI effects at 1,500 mg
TIMES 1	213 Japanese patients; 1,000 mg twice daily vs placebo; 24 weeks	HbA1c -0.72% with imeglimin vs +0.15% placebo; difference -0.87% (95% CI -1.04 to -0.69). Fasting glucose difference about -18.5 mg/dL (-1.03 mmol/L)	Short, selected population; no active comparator
TIMES 2	714 Japanese patients; open-label monotherapy or add-on; 52 weeks	HbA1c change: monotherapy -0.46%; add-on range -0.12% to -0.92% depending on background drug	Uncontrolled; groups differ in baseline disease and cannot be ranked against each other
TIMES 3	215 Japanese insulin-treated patients; 16-week placebo-controlled phase plus 36-week extension	Week 16 difference -0.60% (95% CI -0.80 to -0.40); reduction maintained to week 52	Hypoglycaemia increased with insulin; no hard outcomes
FAMILIAR, 24 weeks	117 randomised Japanese patients inadequately controlled on a DPP-4 inhibitor	HbA1c -0.65% with imeglimin vs +0.38% placebo; difference -1.02% (95% CI -1.33 to -0.72)	Small; highly selected population
FAMILIAR, 104 weeks	80-week open-label extension after the controlled phase; 81 completed	Early-start group change -0.55% at week 104; elderly subgroup -0.58%	After week 24 there was no placebo control; attrition and Japanese lean phenotype limit generalisation
MEGMI	65 Japanese patients on DPP-4 inhibitor plus low-dose metformin; open-label randomised add-on imeglimin vs metformin escalation; 24 weeks	Between-group HbA1c change difference -0.21% favouring imeglimin (95% CI -0.41 to -0.01)	Very small and open-label; seven imeglimin patients discontinued for serious GI events
Caucasian phase 2 add-on studies	1,500 mg twice daily added to metformin or sitagliptin for 12 weeks	Placebo-adjusted HbA1c reductions about -0.44% and -0.72%, respectively	Short and used a non-marketed higher dose

Sources: phase 2b, TIMES 1, TIMES 2, TIMES 3, FAMILIAR 24-week report, FAMILIAR 104-week report, MEGMI.

4.2 Interpretation of effect size

The most credible estimate at the marketed dose is a **placebo-adjusted HbA1c fall of about 0.6-0.9 percentage points**, with larger reductions when baseline HbA1c is higher or when the comparator group deteriorates. This is clinically useful but not exceptional among glucose-lowering drugs.

The 52-week TIMES 2 combination results should not be interpreted as evidence that DPP-4 inhibitors or thiazolidinediones are the “best” partners. The GLP-1 receptor agonist subgroup’s small -0.12% change likewise does not prove antagonism; those patients had longer-duration, more advanced diabetes and the study was neither randomised between background therapies nor placebo-controlled.

Weight is usually neutral in randomised trials. Some uncontrolled real-world studies report modest weight or lipid improvements, but these are vulnerable to concurrent treatment changes, regression to the mean and lifestyle effects. Imeglimin is not a weight-loss drug.

4.3 What has not been shown

No completed trial has established that imeglimin:

- reduces myocardial infarction, stroke, cardiovascular death or heart-failure admission;
- slows eGFR decline, reduces albuminuria sufficiently to predict benefit, or prevents dialysis;
- reduces all-cause mortality;
- prevents progression from prediabetes;
- is superior to metformin as first-line therapy;
- is superior to SGLT2 inhibitors or GLP-1 receptor agonists for any patient-important outcome; or
- durably preserves human beta-cell mass.

This distinction matters because HbA1c efficacy alone no longer defines the preferred therapy for patients with atherosclerotic cardiovascular disease, heart failure, chronic kidney disease or obesity.

5. Safety and tolerability

5.1 Gastrointestinal effects

Nausea, diarrhoea, constipation, vomiting, abdominal discomfort, dyspepsia and reduced appetite are the characteristic adverse effects. They are often early and mild to moderate, but can lead to discontinuation.

Dose matters. In the Japanese phase 2b study, drug-related adverse events were about 5% at 500 or 1,000 mg twice daily but 24% at 1,500 mg twice daily; nausea, abdominal discomfort, diarrhoea and vomiting accounted for the difference. Combination with metformin is particularly troublesome. In TIMES 2, 37.5% of the metformin/biguanide subgroup had a treatment-related adverse event, with diarrhoea in 15.6%, nausea in 10.9% and vomiting in 4.7%.

The **January 2026 Japanese label added severe appetite loss and vomiting, with cases progressing to dehydration, as serious adverse reactions of unknown frequency**. Persistent vomiting, inability to eat or drink, or dehydration therefore warrants prompt medical review rather than simply “pushing through” the symptoms. Current Japanese label

5.2 Hypoglycaemia

Imeglimin alone has a low hypoglycaemia risk because its insulin-secretory effect is glucose-dependent. In TIMES 1, hypoglycaemia occurred in approximately 1.9% with imeglimin and 0.9% with placebo; no severe episode occurred.

Risk rises with other glucose-lowering therapies. In the 52-week insulin study, 21.3% of continuously treated participants had hypoglycaemia, although no severe event was reported. In TIMES 2, rates were highest with sulfonylureas and glinides. The Japanese label advises considering a reduction in insulin, sulfonylurea or rapid-acting secretagogue doses when imeglimin is added.

5.3 Lactic acidosis and blood lactate

No lactic-acidosis event occurred in the pre-approval clinical programme, and animal experiments suggest less propensity than metformin to raise lactate under comparable stress. That does **not** prove zero risk. PMDA noted that the trials were too small to quantify a rare event, excluded many high-risk patients, and included occasional sustained increases in blood lactate. Lactic acidosis remains an “important potential risk” because imeglimin shares some mitochondrial and gluconeogenic pharmacology with biguanides. PMDA review report, comparative animal study

Clinical caution is especially sensible during acute kidney injury, severe dehydration, sepsis, hypoxia, decompensated heart or respiratory failure, severe hepatic disease or heavy alcohol exposure. Those are not proof that imeglimin causes lactic acidosis, but they reduce physiological reserve and can markedly increase drug exposure or lactate production. Acute serious illness should trigger clinician-led "sick day" review of all diabetes medication.

5.4 Other safety issues

- **Serious illness and surgery:** the Japanese label contraindicates use in severe infection, around surgery, or major trauma, where insulin-based management is preferred.
- **Type 1 diabetes, severe ketosis or diabetic coma:** contraindicated; imeglimin is not a substitute for insulin.
- **Cardiac electrophysiology:** a thorough-QT study did not identify clinically important QT prolongation, even at supratherapeutic single doses.
- **Pancreatitis, ketoacidosis, oedema and genitourinary infection:** no consistent class signal comparable with GLP-1 receptor agonists, SGLT2 inhibitors or thiazolidinediones has emerged, but the exposed population and follow-up remain much smaller than for established global drugs.
- **Retinopathy/macular oedema and bladder infection:** listed as uncommon reactions in the Japanese label; causality and magnitude are uncertain.
- **Long-term malignancy risk:** nonclinical testing did not generate a prominent signal, but human exposure is too limited to detect very rare or long-latency effects confidently.
- **Overdose:** there is no specific antidote and no clinical evidence defining dialysis clearance; treatment is supportive and requires urgent toxicology/medical advice.

6. Kidney function: accumulation, dosing and evidence

Kidney function is a central determinant of imeglimin exposure. In single-dose studies, AUC was about 1.49-fold higher with mild impairment, 1.81-fold higher with moderate impairment and 2.49-fold higher with severe impairment than with normal function. During 500 mg twice-daily repeat dosing, AUC was 3.56-fold higher in the severe creatinine-clearance group.

Current Japanese renal dosing

eGFR (mL/min/1.73 m²)	Current Japanese regimen	Evidence caveat
≥45	1,000 mg twice daily	Standard marketed regimen
15 to <45	500 mg twice daily	Supported by exposure modelling and TWINKLE
10 to <15	500 mg once daily	Only two participants contributed pharmacokinetic estimates; use only when benefit outweighs risk, with frequent monitoring
<10, including dialysis	Not recommended	No dialysis-removal study and essentially no clinical efficacy/safety evidence

The 2025 TWINKLE phase 4 study enrolled 60 Japanese patients with eGFR below 45: 42 had G3b, 16 had G4 and only two had G5 kidney disease. It was open-label and had no control group. Adverse events occurred in 68.3%, with no evident new safety pattern; all ten serious events were judged unrelated by investigators. Mean HbA1c fell about 0.53% at week 24 and 0.26% at week 52 with last observation carried forward. These findings supported the 2025 label expansion, but they do not establish kidney protection and offer extremely thin evidence near eGFR 10-15. TWINKLE report, 2025 label expansion

An eGFR is not a fixed personal constant. Dehydration, intercurrent illness, NSAIDs, haemodynamic changes and laboratory variability can move a patient across a dose threshold. A dose decision should therefore use a recent result and its trend, not a historical isolated value.

7. Hepatic impairment and special populations

- **Hepatic impairment:** in seven participants with Child-Pugh B disease, Cmax rose 29% and AUC 47% after a single dose. Severe Child-Pugh C disease has not been studied.
- **Older adults:** pooled pharmacokinetic modelling estimated about 28% higher exposure in people 65 or older. The 104-week FAMILIAR extension is reassuring for selected older Japanese patients, but kidney function, frailty and nutrition require attention.
- **Pregnancy:** the Japanese label says not to use imeglimin in pregnancy or when pregnancy is possible and recommends insulin instead. Placental transfer and embryo-fetal toxicity occurred in animals at relevant-to-high exposures.
- **Breastfeeding:** human data are absent; transfer into rat milk occurred. The label calls for an individual decision about continuing breastfeeding or treatment.
- **Children and adolescents:** no adequate trials; safety and efficacy are unestablished.

8. Drug interactions

Imeglimin has little CYP interaction potential. Dedicated studies found:

- sitagliptin AUC and Cmax rose about 13% and 15%; not clinically important;
- metformin AUC and Cmax fell about 14% and 10%; not clinically important pharmacokinetically;
- cimetidine increased imeglimin AUC and Cmax about 27% and 34%; judged not clinically important in healthy volunteers; and
- population modelling found similar imeglimin exposure with common glucose-lowering drugs, including dapagliflozin and empagliflozin.

The more important interactions are **pharmacodynamic**:

- insulin, sulfonylureas and glinides increase hypoglycaemia risk;
- metformin adds substantial gastrointestinal intolerance and may compound concern during dehydration or renal deterioration;
- GLP-1 receptor agonists can add nausea, vomiting and poor intake;
- SGLT2 inhibitors can contribute to volume depletion during acute illness; and
- beta-blockers may blunt adrenergic warning symptoms of hypoglycaemia.

The absence of a documented interaction is not proof that every combination is safe. OCT2/MATE inhibitors could theoretically raise exposure, and polypharmacy requires a patient-specific review.

9. Comparison with metformin and contemporary alternatives

Feature	Imeglimin	Metformin	SGLT2 inhibitor	GLP-1 receptor agonist / dual incretin
Main demonstrated benefit	HbA1c lowering	HbA1c lowering; extensive long-term experience	HbA1c plus heart-failure/kidney benefits for appropriate drugs/populations	HbA1c, major weight loss; cardiovascular benefit for appropriate drugs
Typical weight effect	Neutral	Neutral or small loss	Small loss	Moderate to very large loss
Hypoglycaemia alone	Low	Low	Low	Low
Common tolerability issue	GI, especially with metformin	GI; B12 deficiency over time	Genital infection, volume depletion; ketoacidosis risk	GI; gallbladder disease and other class cautions
Renal elimination	Important; dose reduction required	Important; eGFR restrictions	Drug-specific, with kidney indications extending to low eGFR	Variable by agent
Cardiovascular/kidney outcome evidence	None	Historical/observational and limited trial evidence	Strong for indicated agents	Strong for indicated agents
Longevity evidence	None	Suggestive epidemiology/preclinical work, not proof	None as an anti-ageing therapy	None as an anti-ageing therapy

Imeglimin’s distinctive advantage is its combination of glucose-dependent beta-cell action and mitochondrial/redox pharmacology. Its disadvantage is that it enters a mature therapeutic field without the cardiovascular, renal, obesity or mortality outcome evidence that drives contemporary treatment selection. For a person with heart failure, established atherosclerotic disease, chronic kidney disease or obesity, current evidence usually gives SGLT2 inhibitors and/or GLP-1-based therapies a stronger outcome-based rationale, subject to individual contraindications and tolerability.

Imeglimin may still have a rational niche for a patient who needs additional modest HbA1c lowering, values weight neutrality and low intrinsic hypoglycaemia, cannot tolerate more metformin, or is unsuitable for other drugs. That is a clinical positioning argument-not proof of superiority.

10. Experimental organ-protective and non-diabetes findings

Cardiovascular and endothelial models

Imeglimin has reduced endothelial oxidative stress, delayed mitochondrial permeability-transition-pore opening and improved endothelial or diastolic measures in diabetic/stressed animal models. A metabolic-syndrome rat study reported attenuation of cardiac and renal structural/functional injury after short- and long-term dosing. These are biologically plausible but do not substitute for a human cardiovascular-outcome trial. Cardiorenal rat study

Liver disease

Animal work suggests improvement in steatosis, oxidative injury and mitochondrial lipid handling. Small clinical studies in type 2 diabetes with metabolic dysfunction-associated steatotic liver disease have reported improvements in some liver enzymes and fibrosis/inflammation markers, but not consistent reductions in liver fat or stiffness. Imeglimin is not an authorised treatment for MASLD/MASH. Clinical MASLD study

Kidney, nervous system and inflammation

Experimental papers report reduced diabetic kidney injury, inflammasome activity, neuropathy and brain mitochondrial dysfunction. These are hypothesis-generating. Doses, exposures and disease models vary, and no clinical trial has shown prevention of kidney failure, neuropathy progression or cognitive decline.

HbA1c interpretation and erythrocyte lifespan

A small 2025 single-arm exploratory study suggested that imeglimin may reduce erythrocyte oxidative stress and lengthen red-cell survival. If confirmed, HbA1c could fall less-or even appear relatively higher-than glycated albumin or directly measured glucose would predict early in treatment. This concerns **red-cell lifespan, not organism lifespan** and should not be misrepresented as longevity evidence. INFINITY exploratory study

11. Imeglimin and longevity

What makes the hypothesis interesting

Imeglimin intersects several pathways discussed in ageing biology:

- mitochondrial electron-flow and redox control;
- suppression of RET-derived ROS;
- NAD+ salvage/signalling;
- AMPK activation in some tissues;
- mPTP stability and reduced apoptosis;
- mitophagy/mitochondrial quality control; and
- improved glucose homeostasis, which could indirectly reduce diabetic complications.

Why that does not constitute longevity evidence

As of 27 August 2026, there is no published evidence that imeglimin extends median or maximum lifespan in worms, flies, normal mice or humans. There is no accepted human trial showing reduced frailty, multimorbidity or mortality in non-diabetic people. A community-written proposal to test imeglimin in the US National Institute on Aging Interventions Testing Program is a proposal, not an experiment or an accepted programme result.

There are also plausible counterarguments. Chronic respiratory-chain constraint may not be beneficial in every tissue or physiological state; many mechanistic experiments use supra-physiological concentrations; amplified insulin secretion is not obviously calorie-restriction mimetic; and improved glucose control in diabetic models can make downstream “anti-ageing” biomarkers look better without altering intrinsic ageing.

The current longevity verdict is therefore **mechanistically intriguing, empirically untested and unsuitable as a basis for self-experimentation**. Any benefit in a person with diabetes would first be expected to come from appropriate glycaemic control, not from a demonstrated anti-ageing action.

12. Quality and limitations of the evidence base

Strengths

- Multiple randomised, double-blind, placebo-controlled trials show consistent HbA1c lowering.
- The glucose-dependent secretory mechanism is supported by convergent biochemical, islet and clinical data.
- The Japanese post-marketing programme now includes renal-impairment dosing and more than two years of controlled/open-label follow-up in selected settings.
- The drug has low protein binding, negligible metabolism and relatively few conventional pharmacokinetic interactions.

Weaknesses

- Most pivotal participants were Japanese and relatively lean; generalisability to ethnically diverse, markedly insulin-resistant or severely obese populations is uncertain.
- The controlled periods were generally 12-24 weeks; longer studies were open-label.
- Total exposure is small compared with metformin, SGLT2 inhibitors, DPP-4 inhibitors or GLP-1 receptor agonists.
- Several major trials and many mechanistic studies were sponsor-funded or included sponsor employees.
- No cardiovascular, renal or mortality outcome trial has been completed.
- Severe kidney disease data rest on very small numbers, especially below eGFR 15.
- Much of the organ-protective and mitochondrial narrative comes from cells and disease-model rodents, sometimes at concentrations far above clinical plasma exposure.
- There is no robust evidence for off-label prevention, obesity treatment, neuroprotection or longevity.

13. Practical clinical checklist

For a legitimate diabetes indication, a prescribing clinician would ordinarily clarify:

1. Is type 2 diabetes confirmed, and what is the HbA1c/glucose target?
2. What is the most recent eGFR and its trend? Has there been recent dehydration or acute kidney injury?
3. Is the patient taking insulin, a sulfonylurea or a glinide that might need reduction?
4. Is metformin or a GLP-1 drug already causing nausea, diarrhoea, vomiting or poor intake?
5. Is there pregnancy, breastfeeding, severe liver disease, hypoxia, heavy alcohol use, major infection, surgery or trauma?
6. Are cardiovascular disease, heart failure, kidney disease or obesity present-conditions for which another drug may have proven outcome benefits?
7. Will HbA1c and fasting/home glucose be reassessed at about three months, with treatment changed if ineffective?

8. Does the patient know to seek help for severe vomiting, poor intake, dehydration or recurrent hypoglycaemia?

Importing an unlicensed product into the UK introduces additional uncertainties about legality, product provenance, strength, formulation, monitoring and responsibility for adverse events. It is particularly inappropriate for longevity self-experimentation.

Bottom line

Imeglimin is a genuine and pharmacologically interesting diabetes medicine-not hype-but the strongest evidence is narrower than the mitochondrial narrative suggests. At the marketed dose it lowers HbA1c by roughly 0.6-0.9 percentage points, is usually weight-neutral, and has low intrinsic hypoglycaemia risk. Its principal liabilities are gastrointestinal intolerance, increased hypoglycaemia with insulin/secretagogues, renal accumulation and a much smaller long-term safety/outcomes database than older or globally used alternatives.

Its modulation of beta-cell NAD+ signalling, Complex I reverse-electron-transport ROS, mitochondrial permeability transition and mitophagy makes it unusually interesting scientifically. None of that currently demonstrates cardiovascular protection, kidney protection or lifespan extension. For diabetes it can be a rational clinician-selected option where licensed; for longevity it remains an unsupported experiment.

Selected primary and regulatory sources

1. PMDA review report for Twymeeg
2. Current Japanese product information (2026 revision)
3. Imeglimin pharmacology and mechanism review
4. NAD+ salvage and glucose-stimulated insulin secretion
5. Hepatic gluconeogenesis and respiratory-chain kinetics
6. Complex I reverse-electron-transport ROS and mPTP
7. Beta-cell mitochondrial quality and mitophagy
8. TIMES 1 placebo-controlled phase 3 trial
9. TIMES 2 52-week monotherapy/add-on study
10. TIMES 3 insulin add-on trial
11. FAMILIAR 104-week report
12. TWINKLE renal-impairment study