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Imeglimin in Type 2 Diabetes: Expert Consensus in the Indian Context

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Introduction

Type 2 diabetes mellitus (T2DM) is a growing epidemic in India, with an estimated 77 million adult patients – the second highest in the world . Managing T2DM is challenging due to its dual pathophysiology: insulin resistance and β-cell dysfunction . Metformin has long been the first-line oral therapy targeting insulin resistance, but many patients eventually require additional agents as β-cell function declines. Moreover, some patients cannot tolerate or use metformin due to contraindications (e.g. advanced kidney disease, gastrointestinal intolerance). This has created a need for new therapies that address both core defects of T2DM [1].

Imeglimin is a novel oral antidiabetic drug (first in the "glimin" class) that was recently approved in Japan and in India (approved by Indian regulators in October 2022). The purpose of this article is to introduce imeglimin to Indian clinicians and summarize expert opinions on where it fits in the current T2DM treatment algorithm. We review its mechanism of action, key clinical trial data (TIMES program), real-world evidence in India, and consensus recommendations by leading Indian diabetologists on its use in practice. The goal is to provide a practical guide for physicians on utilizing imeglimin in the Indian context, including comparisons with other oral antidiabetic drugs and considerations of cost and patient selection [2].

Mechanism of Action of Imeglimin

Imeglimin has a unique dual mode of action targeting both major abnormalities in T2DM. Firstly, it improves insulin action in peripheral tissues (insulin sensitizer), and secondly, it enhances pancreatic β-cell function. At the cellular level, imeglimin acts as a mitochondrial bioenergetics' modulator. It partially inhibits mitochondrial respiratory chain complex I while restoring complex III activity, which increases ATP generation and reduces excessive reactive oxygen species (ROS) production. Through this modulation, imeglimin reduces hepatic gluconeogenesis (via complex I inhibition) and improves insulin sensitivity in muscle by enhancing insulin-stimulated Akt/PKB phosphorylation, thus promoting glucose uptake [3].

Concurrently, imeglimin benefits the pancreatic islets by improving mitochondrial function in β-cells. Mitochondrial dysfunction is a key factor in β-cell failure; imeglimin helps amplify glucose-stimulated insulin secretion and protects β-cells from oxidative stress and apoptosis. This translates into better preservation of β-cell mass and function. In addition, imeglimin has been associated with reduced hepatic steatosis (fat accumulation in liver) in preclinical studies, which may be an added benefit for T2DM patients who often have fatty liver. By addressing both insulin resistance and insulin secretion, imeglimin tackles the "two concerns" of T2DM in a single therapy. Importantly, its insulinotropic effect is glucose-dependent, meaning it enhances insulin release primarily when glucose is elevated, reducing the risk of hypoglycemia. This multifaceted mechanism distinguishes imeglimin from other oral agents that typically target either insulin resistance (like metformin) or insulin secretion (like sulfonylureas), but not both [4].

Clinical Efficacy: Key Trials (TIMES Program)

The efficacy of imeglimin has been demonstrated in the global TIMES clinical trial program (Trials of IMeglimin for Efficacy and Safety) conducted in Japanese patients, as well as in emerging studies elsewhere. These trials show that imeglimin provides significant glucose lowering comparable to other oral antidiabetics, with a favorable safety profile.

- TIMES 1 (Monotherapy vs Placebo): In a 24-week Phase 3 trial, imeglimin 1000 mg twice daily as monotherapy

reduced HbA1c by ~0.8–0.9% more than placebo in treatment-naïve Japanese T2DM patients . Baseline HbA1c in this trial was relatively modest (~7.7%), yet imeglimin achieved nearly a 1% absolute drop vs placebo. Notably, the participants included many older patients and those with mild renal impairment, factors that usually attenuate glycemic response . The trial confirmed that imeglimin monotherapy significantly improves glycemic control with a placebo-like safety profile (overall adverse event rates ~44% in both imeglimin and placebo groups) .

- TIMES 2 (Long-term Safety and Combination Therapy): This was a 52-week study (the largest of the Phase 3 program) assessing imeglimin 1000 mg BID as monotherapy or in combination with other agents. About half the participants were elderly, and a majority had mild-to-moderate chronic kidney disease (stage 2 CKD in ~73%, stage 3A in ~18%) . Over 1 year, no hypoglycemia was seen with imeglimin monotherapy, and glycemic reductions were sustained . When imeglimin was added to other drugs (like sulfonylureas or insulin), hypoglycemic events were only slightly increased, indicating that imeglimin itself does not provoke hypoglycemia . This trial demonstrated sustained efficacy and safety of imeglimin in a real-world mix of patients, including older and renally impaired individuals. It also underscored that imeglimin can be safely used in mild-to-moderate renal dysfunction, though it should be avoided once eGFR <30 mL/min/1.73m² (similar to metformin restrictions) .
- TIMES 3 (Add-on to Insulin): In T2DM patients inadequately controlled on insulin alone, adding imeglimin achieved further HbA1c reduction of about −0.6% vs placebo after 16 weeks. This improvement occurred without an increased risk of adverse events compared to placebo. The TIMES 3 results indicate imeglimin is effective as an add-on to insulin therapy, helping lower glucose in insulin-resistant patients while potentially allowing reduction of insulin dosage (though insulin dose adjustments were not detailed in the initial 16-week double-blind phase). A 36-week open-label extension showed continued glycemic control with imeglimin plus insulin and maintained safety over the longer term.

Beyond these pivotal trials, a meta-analysis of earlier randomized studies confirmed that imeglimin significantly improves glycemic control and β-cell function with a good safety profile. Overall, imeglimin's HbA1c-lowering efficacy (~0.6–1.0% reduction) is on par with DPP-4 inhibitors and SGLT2 inhibitors, slightly less than metformin's typical ~1.0–1.5% reduction in drug-naïve patients. However, given that imeglimin trials often included older patients or those with comorbidities, the glucose reduction is clinically meaningful. Furthermore, imeglimin has shown ancillary benefits such as modest weight loss in some studies (discussed below), differentiating it from certain other classes.

Real-World Evidence in India

Since its approval in India in late 2022, imeglimin has been adopted by clinicians and studied in real-world settings. A large multicenter retrospective study (INDI-TIMES, 2024) evaluated over 8,300 Indian T2DM patients who were started on imeglimin 1000 mg BID in routine practice. These patients were diverse (some treatment-naïve, others on background antidiabetic drugs) with baseline HbA1c between 7% and 9%. After 3 months of imeglimin therapy (alone or added to existing regimens), there were significant improvements in glycemic parameters [5-10].

- HbA1c: Mean reduction of 1.12% from baseline (e.g. from ~8.5% to ~7.4%) . Nearly 45% of patients achieved HbA1c <7% within 3 months, which is impressive for a predominantly add-on therapy cohort.
- Fasting Plasma Glucose: Decreased by ~29 mg/dL, and postprandial glucose reduced by ~62 mg/dL on average.
- Body Weight: A modest mean weight loss of about 2.0 kg was observed over 3 months. This suggests that imeglimin is at least weight-neutral and possibly helps a bit with weight reduction, an advantage over therapies like sulfonylureas or insulin which tend to increase weight.
- Safety: Notably, no significant adverse events were reported in this large cohort. The drug was well-tolerated, and no patients had to discontinue due to side effects in the observation period. Such tolerability in thousands of patients underscores imeglimin's real-world safety. The authors also noted improvements in some metabolic parameters (lipid profile, hepatic enzymes, blood pressure), though those findings were preliminary.

These Indian findings align with global trial data, reinforcing that imeglimin is an effective and well-tolerated option for managing T2DM in a typical Indian patient population. Importantly, this study highlighted imeglimin's utility across various patient subgroups (different ages, baseline glucose levels, monotherapy vs combination). It provided local clinicians with confidence that the drug works outside of controlled trials and can be integrated into practice. Going forward, prospective Indian studies and registries are anticipated to further clarify imeglimin's long-term impact on glycemic control and diabetes complications in India.

Safety and Tolerability Profile

Imeglimin's safety profile is a major strength, especially for patient groups that are sensitive to side effects. Clinical trials have consistently shown no increase in overall adverse events vs placebo. In TIMES 1, for example, adverse events were reported by ~44% of patients in both imeglimin and placebo arms, with no significant differences . Most side effects were mild. Crucially, hypoglycemia risk with imeglimin is minimal – it does not induce low glucose on its own due to its glucose-dependent mechanism of insulin enhancement. No hypoglycemia was seen with monotherapy in long-term trials , and even when combined with insulin or sulfonylureas, hypoglycemia incidence only slightly increased relative to placebo (appropriate precautions still should be taken when combining with those agents) [11-15].

Gastrointestinal (GI) tolerability appears to be superior with imeglimin compared to metformin. Metformin's common side effects (nausea, diarrhea, abdominal discomfort) limit its use in some patients. In contrast, experts have noted that imeglimin

causes fewer GI issues . For instance, it is less likely to provoke significant nausea or diarrhea; one real-world advantage is that imeglimin can be given at full effective doses without a lengthy titration phase that metformin often requires to mitigate GI upset. A minority of patients may experience mild side effects such as constipation or dizziness, but these are infrequent and generally not severe . An Indian consensus review highlighted that in practice imeglimin is well tolerated even in those who had difficulty with metformin's side effects. In the Indian 8300-patient study, no notable adverse effects were reported, underscoring tolerability [16].

One safety consideration is use in patients with renal impairment. Imeglimin is renally excreted, and while it has been shown to be safe in mild-to-moderate CKD (e.g. eGFR 30–60 mL/min) , it is not recommended in advanced kidney disease. Similar to metformin, imeglimin should be discontinued if eGFR falls below 30 mL/min/1.73m² . Unlike metformin, however, imeglimin is not associated with lactic acidosis, so the primary concern in CKD is accumulation of the drug leading to higher exposure, rather than any known nephrotoxicity or lactic acidosis. There is ongoing research on appropriate dosing in renal impairment; one approach by manufacturers is to possibly develop a lower dose for severe CKD, but currently the conservative approach is to avoid imeglimin in eGFR <30 [17].

Imeglimin has no known serious chronic safety issues so far. No signal for hepatic toxicity has emerged, and it does not seem to cause edema or heart failure (unlike TZD class) or any pancreatitis risk (unlike GLP-1 or DPP-4 therapies). Preclinical studies even suggest it may have protective effects on cardiac and renal tissues through mitochondrial mechanisms , though clinical proof of cardiovascular benefit is not yet established. Overall, the tolerability profile of imeglimin – especially its use in metformin-intolerant patients – makes it a valuable addition. For an elderly patient or one with frailty, the lack of hypoglycemia and minimal side effects are particularly important. Likewise, patients who experienced GI issues on metformin often tolerate imeglimin much better, allowing them to still address insulin resistance without discomfort [18-20].

Placement of Imeglimin in Therapy (Indian Expert Consensus)
Shortly after imeglimin's introduction, Indian endocrinologists and diabetologists convened to share clinical experiences and formulate consensus guidance for its use . Multiple advisory board meetings with key opinion leaders across India were held, culminating in a consensus paper (Seshadri et al., JAPI 2025) that provides practical recommendations . According to these expert opinions, imeglimin's ideal place in therapy can be summarized as follows:

- First-line Alternative to Metformin: Imeglimin can be used as monotherapy in newly diagnosed T2DM patients when metformin is contraindicated or not tolerated . Experts agreed that if a patient has significant metformin intolerance (persistent GI side effects) or a contraindication (e.g. CKD stage 3b or 4, where metformin use is limited), imeglimin is a suitable first-line agent to achieve glycemic control. It addresses both insulin resistance and β-cell dysfunction like metformin does (and more), but with better GI tolerability. Thus, imeglimin fills an important gap for patients who cannot use metformin .
- Add-On to Oral Drugs: For patients not at target on metformin alone, or on other oral agents, imeglimin is recommended as an add-on therapy. The consensus indicated that imeglimin works well in combination with other oral antidiabetic drugs such as DPP-4 inhibitors (gliptins) or SGLT2 inhibitors . In real-world practice, an example would be a patient on metformin and a DPP-4 inhibitor who still has suboptimal control – adding imeglimin could further reduce HbA1c by ~0.6–0.8% without additional side-effect burden. Combination of imeglimin with SGLT2 inhibitors is also rational: SGLT2 inhibitors promote urinary glucose excretion and weight loss, while imeglimin improves insulin sensitivity/secretion, and both have complementary effects with low hypoglycemia risk. Early clinical experience has shown additive glycemic benefits with these combinations, and they can be considered in patients who cannot afford or do not need injectable therapies like GLP-1 agonists.
- Add-On to Insulin: In insulin-requiring T2DM patients (e.g. long-standing diabetes with β-cell exhaustion), adding imeglimin can provide incremental improvement in glucose control . The consensus experts noted that in patients on basal insulin or premix insulin, introducing imeglimin may help lower fasting and postprandial glucose further, potentially allowing a reduction in insulin dose or at least preventing dose escalation. This is especially useful in overweight patients on insulin, as imeglimin may aid weight stability (whereas increasing insulin dosage often causes weight gain). Additionally, the lack of intrinsic hypoglycemia with imeglimin means it can be added without significantly raising the risk of low blood sugars, though careful monitoring is still advised.
- Use in Elderly and Comorbid Patients: The panel highlighted that imeglimin is well-suited for elderly patients, who often have multiple comorbidities and higher risk of side effects. In the elderly, metformin can cause anorexia or B12 deficiency and sulfonylureas pose hypoglycemia risks; imeglimin offers an option with mild side effects and low hypo risk, and was shown effective even in patients over 65 in trials. Similarly, in patients with mild heart failure or liver dysfunction, imeglimin has not shown any contraindications (unlike some other agents), though robust data in these groups are still forthcoming. Its use in moderate CKD (eGFR 30–60) was supported by experts, with the understanding that renal function should be monitored over time.
- Combination with Metformin: Interestingly, while imeglimin can substitute for metformin, it has also been used alongside metformin in cases where metformin alone is insufficient. Some studies have explored adding imeglimin to patients already on metformin to further improve glycemic control instead of upping the metformin dose or moving to insulin . The combination can yield additional HbA1c reductions beyond what metformin provides . However, the consensus cautioned to watch for GI side effects in such dual therapy – since both drugs act on mitochondria and

metabolism, some patients might experience nausea or GI discomfort when high-dose metformin and imeglimin are used together . Titrating one or both agents slowly can mitigate this. In practice, if metformin is at a moderate dose and not controlling sugar, adding imeglimin (rather than maxing out metformin) could be a viable strategy, balancing efficacy and tolerability.

These consensus recommendations position imeglimin as a flexible agent in the T2DM arsenal: either as an alternative foundation therapy (when metformin can't be used) or as an add-on to nearly any regimen lacking control. The overriding theme from Indian experts is that imeglimin should be considered in scenarios of unmet needs – e.g., patients who have dual defects of insulin resistance and insulinopenia, those who are intolerant to existing medications, or those who need extra glycemic lowering without added side-effect burden. The consensus did not advocate replacing metformin in all patients, but rather using imeglimin to fill therapeutic gaps and to personalize therapy for better outcomes [21-28].

Comparison with Other Oral Antidiabetic Drugs

Metformin vs Imeglimin: Metformin remains the cornerstone of T2DM management due to its long-term data and cost-effectiveness. Imeglimin shares some of metformin's beneficial attributes – both target hepatic gluconeogenesis and improve insulin sensitivity – but imeglimin also directly supports β-cell insulin secretion . In head-to-head comparisons, metformin tends to have a slightly greater initial HbA1c reduction (especially in high-baseline A1c patients) . For example, a classic trial showed metformin could lower A1c by ~1.4% vs placebo, whereas imeglimin in a similar Japanese trial lowered it by ~0.8% vs placebo . However, differences in patient populations (imeglimin trials had older patients, some renal impairment) make direct efficacy comparisons nuanced . In a Phase 2 study by Pirags et al., imeglimin 1500 mg BID was found to be as effective as metformin 850 mg BID in reducing glucose levels over 8 weeks [29, 30].

Tolerability is where imeglimin can have an edge: it generally causes fewer GI side effects than metformin and does not carry a risk of lactic acidosis. Thus, in patients who cannot reach metformin's optimal dose due to GI intolerance, switching to or adding imeglimin could achieve better glycemic control. Both drugs are weight-neutral or modestly weight-reducing. Neither causes hypoglycemia by itself. Importantly, metformin has proven cardiovascular benefits in certain subsets (overweight newly diagnosed patients, per UKPDS data), whereas imeglimin's cardiovascular effects are still being studied. Preclinical models suggest cardio-renal protective effects of imeglimin , but no cardiovascular outcome trial (CVOT) has been completed yet. In summary, metformin remains first-line for most, but imeglimin is a strong alternative when metformin is unsuitable, and a potential adjunct in metformin partial responders [31, 32].

DPP-4 Inhibitors (Gliptins) vs Imeglimin: DPP-4 inhibitors like sitagliptin, vildagliptin, etc., primarily act by enhancing incretin hormones to increase insulin release and suppress glucagon when glucose is high. Their A1c reduction is around 0.6–0.8%, similar to imeglimin's. Both DPP-4is and imeglimin are weight-neutral and have low hypoglycemia risk. One difference is that imeglimin improves insulin sensitivity in muscle and liver (which gliptins do not directly do), and imeglimin has a more direct effect on β-cell mitochondria. There is interest in combining a gliptin with imeglimin – mechanistically, this could provide a complementary effect (incretin pathway + mitochondrial pathway).

A recent study (MEGMI trial) in Japan found that adding imeglimin to a DPP-4 inhibitor (with low-dose metformin) improved A1c more than uptitrating metformin . This suggests imeglimin can be a useful add-on to DPP-4 inhibitors in patients who need additional control. In terms of side effects, DPP-4 inhibitors are very well tolerated; imeglimin is also well tolerated, so combination therapy is generally easy to administer. Cost-wise, many DPP-4 inhibitors are now generic in India, so their prices have come down; imeglimin is new but is also affordably priced (see next section). If a patient has gastrointestinal issues or a history of pancreatitis (a rare risk with DPP-4is), imeglimin could be chosen instead of a gliptin.

SGLT2 Inhibitors vs Imeglimin: SGLT2 inhibitors (e.g. dapagliflozin, empagliflozin) lower blood sugar by promoting glycosuria and have additional benefits of weight loss and blood pressure reduction, plus proven cardiovascular and kidney protection in high-risk patients. Imeglimin does not have such extraglycemic benefits demonstrated yet, and it does not cause weight loss to the same degree. An advantage of imeglimin is that it can be used even when SGLT2 inhibitors are less suitable (for instance, in an elderly patient at risk of genital infections or hypotension from SGLT2is).

Both classes can be used together for synergistic effects. SGLT2 inhibitors have moderate cost and are now recommended for many patients with cardiac or renal comorbidities; imeglimin might not replace an SGLT2i in those specific scenarios, but in purely glycemic terms, if cost or tolerance of SGLT2i is an issue, imeglimin is a reasonable alternative to achieve A1c goals. One should note that imeglimin, being insulin-dependent in action, may not be sufficient in cases of very severe insulin deficiency where insulin or SU or SGLT2i (which works insulin-independently) might be required.

Sulfonylureas vs Imeglimin: Sulfonylureas (glimepiride, gliclazide, etc.) are effective in lowering A1c (~1–1.5%) but at the cost of hypoglycemia and weight gain. Imeglimin offers a non-sulfonylurea secretagogue approach: it enhances insulin secretion only when glucose is high, thus avoiding the risk of hypoglycemia seen with SUs. While sulfonylureas directly force insulin release (even at low glucose), imeglimin works more gently via metabolic modulation. In an algorithm where SUs are traditionally added as second-line (especially in resource-limited settings for cost reasons), imeglimin could be considered a safer alternative second-line agent if available. It may yield slightly less HbA1c reduction than a maximal SU dose, but without the risk of dangerous hypos or additional weight gain. For an older patient living alone, imeglimin is far safer than an

SU from a hypoglycemia standpoint. Indian experts have welcomed imeglimin as a way to possibly reduce sulfonylurea use, given the frequent hypoglycemia issues encountered in primary care with SUs.

In summary, imeglimin occupies a niche somewhat akin to metformin and gliptins, as a safe oral agent with moderate efficacy, but it is unique in tackling both insulin resistance and secretion. It may not replace drugs that have clear cardiovascular/renal outcome benefits (like SGLT2i or GLP-1 agonists) in patients who need those, but it complements the existing options and can be an excellent choice in many typical T2DM patients in India who require dual mechanism correction with minimal side effects [33].

Relevance to the Indian Context

India faces particular challenges in diabetes management, including a high prevalence of young-onset T2DM, limited healthcare resources, and cost constraints. Imeglimin's introduction is timely and pertinent to several of these challenges:

- Addressing Dual Defects: Many Indian patients have a combination of significant insulin resistance (often related to central obesity, urban lifestyles) and early beta-cell dysfunction (sometimes seen in relatively lean T2DM phenotypes or due to late diagnoses). Managing both defects usually required multiple drugs. Imeglimin's ability to concurrently improve insulin sensitivity and β-cell output is advantageous in the Indian context, potentially delaying the need for insulin or multiple drug combinations . As one narrative review put it, T2DM care often boils down to tackling "two concerns" (insulin resistance and secretion) and imeglimin emerges as a "single solution" that targets the disease's mitochondrial roots .
- Metformin Intolerance and Treatment Gaps: While metformin is cheap and effective, a subset of Indian patients (due to dietary habits or genetic predisposition) experience intolerable GI side effects, or have contraindications like renal impairment. Previously, such patients might be started on a sulfonylurea or insulin straightaway, which isn't ideal. Now, imeglimin offers an alternative oral therapy for metformin-intolerant individuals to get similar glycemic benefit without the side effects . Also, in rural or resource-limited settings where close monitoring for hypoglycemia is difficult, using a drug like imeglimin (instead of SU) could improve safety.
- Affordability: Cost is a critical factor in India. Many newer diabetes drugs (GLP-1 analogues, newer insulins) are expensive and beyond reach for a large segment of patients. Imeglimin, being produced by Indian pharmaceutical companies (e.g., Zydus, Torrent, etc.), is priced reasonably. The average cost of imeglimin therapy is approximately ₹25–30 per day (around ₹800–900 per month for a full 1000 mg BID dose), which is comparable to or lower than the cost of DPP-4 inhibitors and much lower than imported newer drugs. This cost advantage means that a broader swath of patients can afford imeglimin. For context, adding an SGLT2 inhibitor or a GLP-1 RA might be financially unfeasible for many, whereas imeglimin can be prescribed with greater confidence that patients will adhere to therapy. The competition among generic manufacturers is likely to drive the price further down over time, solidifying its place in the cost-sensitive Indian market.
- Ease of Use: Imeglimin is taken as an oral pill twice daily (usual dose 1000 mg BID, morning and evening) . It does not require intensive titration (though some physicians start at 500 mg BID for a week or two to ensure tolerance). This is relatively convenient, akin to metformin dosing. In India, where patient education and follow-up can be inconsistent, a therapy that is simple to take and doesn't require complex monitoring (no risk of hypo, no need for periodic dose adjustments unless renal function changes) is very attractive.
- Complement to Lifestyle Interventions: As always, diet and exercise are foundations of diabetes management. In the Indian diet context (high carbohydrate intake), even with lifestyle changes many patients have high postprandial sugars. Imeglimin's enhancement of postprandial insulin secretion helps address that. Experts have noted that imeglimin, alongside lifestyle modification, can help patients reach targets without immediately resorting to polypharmacy.
- In essence, imeglimin fills several gaps in the Indian T2DM management landscape – providing an effective, safe, and affordable option that aligns well with the pathophysiology seen in Indian patients and the practical aspects of care in India.

Limitations and Future Directions

While imeglimin is a promising addition, there are some limitations and open questions:

- Long-term Outcomes: As a new drug, imeglimin lacks long-term outcomes data (e.g. reduction in cardiovascular events or diabetic complications). Metformin, SGLT2i, and GLP-1 RA have robust evidence for improving outcomes beyond glucose control. It remains to be seen if imeglimin can favorably impact cardiovascular or renal outcomes in the long run. Ongoing observational studies and planned trials will need to address this.
- Use in Advanced Disease: Imeglimin's efficacy relies on some residual β-cell function (since it amplifies glucose-dependent insulin release). In very long-standing T2DM or latent autoimmune diabetes of adults (LADA) where β-cells are severely depleted, imeglimin may not be as effective. Such patients will inevitably require insulin; imeglimin is not a replacement for insulin in those who truly need it. Also, in advanced CKD (stage 4-5), imeglimin cannot be used – insulin or other non-renally cleared drugs must be used instead. Thus, imeglimin is not a panacea for all patients.
- Gastrointestinal Combination Effects: Although imeglimin monotherapy has minimal GI issues, when combined with metformin (or potentially with GLP-1 RAs), patients might experience more GI discomfort. Clinicians have anecdotally reported that starting both metformin and imeglimin together in a drug-naïve patient can sometimes cause stomach upset. A prudent approach is to stagger the start or use lower initial doses in combination, to ensure tolerability . More

research is needed on the best combination strategies (for example, should metformin dose be reduced when adding imeglimin if GI side effects emerge?).

- Regulatory and Guideline Inclusion: As of 2025, imeglimin is not yet included in international guidelines (like ADA/EASD consensus) because it's not available globally (approved mainly in Japan and India). Indian national guidelines (RSSDI or API) are expected to update their recommendations to include imeglimin in the coming editions. In the interim, publications like the JAPI consensus serve as a reference for clinicians. Wider acceptance will depend on more published data and post-marketing surveillance to reassure practitioners of its benefits and safety in diverse ethnic groups.
- Special Populations: More data are required in certain groups like pregnant women (metformin is often used in gestational diabetes, but imeglimin is not studied in pregnancy), in type 1 diabetes (where it theoretically could help insulin resistance in overweight type 1s, but no evidence yet), or in combination with GLP-1 agonists (which could be an interesting dual mechanism approach). Research is also looking at imeglimin's role in non-alcoholic fatty liver disease given its effect on hepatic steatosis and recent studies on metabolic-associated fatty liver disease in T2DM showing improved liver inflammation markers.
- Mechanistic Understanding: Although known to target mitochondria, the precise molecular target of imeglimin is still being investigated. A clearer understanding of how it modulates complex I/III and other pathways may open doors to developing more agents in the "glimin" class or combining imeglimin with other modulators for synergistic effects.
- In summary, while imeglimin has some clear benefits, clinicians should use it as part of an individualized treatment plan, considering its appropriate role and the gaps in evidence. Ongoing studies will further define its place in therapy [34].

Conclusion

Imeglimin represents a significant advance in oral diabetes therapy – a dual-acting agent that improves both insulin sensitivity and insulin secretion through novel mitochondrial mechanisms . In the Indian context, where millions of T2DM patients have complex needs and limitations with current treatments, imeglimin offers a fresh approach. Clinical trials (TIMES 1–3) and Indian real-world data have demonstrated that imeglimin can achieve meaningful HbA1c reductions (~1% in many patients) without weight gain or hypoglycemia . Its safety profile is on par with placebo, and it is especially useful in patients who are metformin-intolerant or where other drugs are unsuitable. Indian experts have reached a consensus that imeglimin can be strategically used as monotherapy (when metformin can't be used) or as an add-on to both oral agents and insulin, to help patients reach glycemic goals in a safe manner [35, 36].

For physicians, incorporating imeglimin into practice involves selecting the right patient – for example, an older patient with moderate renal impairment and high postprandial sugars might benefit greatly from imeglimin. The drug's affordability in India further supports its use in wider populations who need effective therapy at reasonable cost. As experience grows, imeglimin may help reduce reliance on sulfonylureas and allow more patients to maintain good control without early progression to injectables [37].

In conclusion, imeglimin is a welcome addition to the T2DM toolkit, particularly suited for India's vast and varied patient pool. It addresses the twin pathophysiologic defects of diabetes in one agent, aligning with the modern paradigm of pathophysiology-based therapy [38-40]. While not a replacement for all existing drugs, it fills important gaps and enhances our ability to tailor treatments. With ongoing research and accumulation of local experience, clearer algorithms will evolve. For now, the expert consensus provides a sound framework: use imeglimin when metformin is not enough or not possible, combine it wisely to harness its unique benefits, and always personalize therapy to the patient's needs. By doing so, Indian clinicians can improve diabetes outcomes leveraging this novel drug, ultimately striving for better control and reduced complications in the burgeoning diabetic population.

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