

# Need of Single Pill Fixed-Dose Combination with Glimepiride in Management of Diabetes Mellitus

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## Abstract

The progressive nature of type 2 diabetes mellitus (T2DM) mostly leads to insufficient glycemic control in people on monotherapy, over long periods of time. This necessitates the requirement of additional agents for achieving the desired glycemic control. Therefore, the use of a combination of drugs is common in the management T2DM. Fixed-dose combinations (FDCs) with single-pill formulations (SP-FDC) of two or more drugs are widely used for effective glycemic control in the management of T2DM, mostly because they reduce pill burden. Glimepiride has emerged to be the drug of choice for SP-FDCs and has widespread use, both as dual-combination SP-FDCs and triple-combination SP-FDCs. Here, we will discuss the need of glimepiride as an FDC component in the management of T2DM, along with clinical evidences on the safety and efficacy of such SP-FDCs.

## Introduction

Lifestyle modifications and monotherapy with oral anti-hyperglycemic drugs are generally considered as the first-line interventions for glycemic control in people with type 2 diabetes mellitus (T2DM). Over the years, with the progression of the disease as the insulin-secreting beta-cells continue to decrease, the efficacy of monotherapy in glycemic control also decreases. This limitation of monotherapy necessitates the requirement of additional agent(s) as combination therapy for the successful management of both hyperglycemia and beta-cell dysfunction. Single Pill Fixed-dose combinations (SP-FDCs) contain multiple hypoglycemic agents formulated as a single-dose form. In general, the most commonly used FDCs are sulfonylurea (SU) with biguanide and thiazolidine with biguanide.<sup>1</sup>

Although there are several advantages of appropriate use of SP-FDCs, their inappropriate or irrational use can lead to serious adverse effects, for example, the individual drug components of the SP-FDC should not interact with each other to avoid chemical instability.<sup>2</sup> Availability of irrational SP-FDCs is a safety risk for people with T2DM. Hence, it is important to ensure the rationality of available SP-FDCs in the market through implementation

of well-designed clinical trials to examine their safety and efficacy prior to their approval. The Government of India banned 344 irrational SP-FDCs in March 2016, which included three of the five top-selling metformin containing SP-FDCs.<sup>3</sup>

## Need and Rationale of SP-FDC in Diabetes Mellitus Management

### Limitations of Monotherapy in T2DM Management

Although newly diagnosed people with T2DM are initially recommended treatment with monotherapy, such as metformin, it often fails to achieve optimum glycemic control in the majority of such people. The progressive nature of T2DM often necessitates the use of multiple glucose-lowering medications for achieving optimum glycemic control. Monotherapy fails to address the complexity and progressive nature of this disease.<sup>4</sup>

### Early and Effective Management of T2DM With Combination Therapy

The traditional 'step-wise' approach to control diabetes mellitus with

lifestyle intervention and monotherapy often delays the achievement and maintenance of glycemic goals. Most often, such delays occur between switching from monotherapy to combination therapy. The step-wise approach also involves uptitration of monotherapy to maximum recommended dose, which is often associated with adverse effects. In contrast, early implementation of combination therapy using submaximal doses of individual hypoglycemic agents improve glycemic control with negligible side effects.<sup>5</sup> In order to compare the safety and HbA<sub>1c</sub> reducing efficacy of glimepiride/metformin combination with metformin uptitration, a randomized, parallel group, open label multicenter study was performed. It was found that as compared to metformin uptitration, glimepiride/metformin combination was well tolerated resulted in more effective glycemic control (adjusted mean decrease in HbA<sub>1c</sub>, -1.2 vs. -0.8%, P < 0.0001) in people with T2DM. Also as compared to metformin uptitration, a higher proportion of SP-FDC group achieved HbA<sub>1c</sub> of <7% (74.7 vs. 46.6%, P < 0.0001).<sup>6</sup>

### Advantage of Single-Pill FDC Over Co-Administered Combination Therapy

Oral combination therapy in people with T2DM may be administered either separately as dispensed individual medications, or as single drug formulations or SP-FDCs. While combination therapy is preferable over monotherapy, even among combination therapies, SP-FDCs are advantageous over multiple-pill combinations. One of the important causes of such advantage of SP-FDCs is that they reduce the complexity of the dosing regimen. This leads to improved patient adherence

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**Table 1: SP-FDCs containing glimepiride in T2DM management**

SP-FDC type	SP-FDC composition
Dual FDC	Metformin + glimepiride <sup>18</sup>
Triple FDC	Metformin + glimepiride + voglibose <sup>18</sup>
	Metformin + glimepiride + pioglitazone <sup>18</sup>

SP-FDC: Single Pill Fixed-dose combination.

to treatment. Secondly, relatively lower doses of individual agents in SP-FDCs might exert greater efficacy than that offered by higher doses or even maximal doses of monotherapy, or that of co-administered combination therapy. Moreover, as compared to multi-pill combination therapy, SP-FDCs potentially provide greater adherence to therapy and improved glycemic control by simplification of treatment and reduction in pill burden along with favorable cost factors.<sup>4</sup> A systematic review of published literature suggested that as compared to people treated with loose pill combination therapy, those treated with SP-FDC therapy might have more satisfaction, improved adherence, and lesser medical costs.<sup>7</sup> Another systematic review of 17 studies (including six studies describing economic data) on people with T2DM reported better healthcare utilization, reduced medical costs, and improved satisfaction in SP-FDCs vs. multi-pill regimens.<sup>4</sup> In a meta-analysis, lower HbA<sub>1c</sub> and higher mean possession ratio values were found to be associated with use of SP-FDCs compared to dual therapies.<sup>8</sup>

### Recommendations for Using Combination Therapy in Diabetes Mellitus Management

As per the recommendations of the International Diabetes Federation, combination therapy with a second glucose-lowering drug should be initiated if monotherapy with metformin or another similar agent fails to reach optimum HbA<sub>1c</sub> target.<sup>9</sup> The Diabetes Canada guideline 2018 recommends the use of combination therapy, since the initiation of therapy in people with T2DM having HbA<sub>1c</sub>  $\geq 1.5\%$  above target.<sup>10</sup> According to the recommendation of the American Diabetes Association, 2019, combination therapy of metformin with other agents including sulfonylurea (SU) should be considered if the target HbA<sub>1c</sub>

is not achieved after three months of therapy, and if chronic kidney disease or cardiovascular disease is not present.<sup>11</sup>

### FDCs With SUs: Focus on Glimepiride

According to the International Diabetes Federation, 2017, SUs have been included in the list of best choice of add-ons in combination therapy, except glibenclamide/glyburide.<sup>3</sup> Sulfonylureas have also been recommended by the Research Society for the Study of Diabetes in India (RSSDI) as the second-line therapy in people with T2DM, when glucose control targets are not achieved by first-line monotherapy based on a patient-centric approach.<sup>12</sup> An International Task Force in its consensus meeting stated that since SP-FDCs containing SUs improve patient adherence, offer convenience and lower cost, SP-FDCs should be made available with different strengths of metformin + SU. It was also stated that the combination of SU + other drugs can also be considered.<sup>13</sup> A combination of metformin, SU, and pioglitazone is the most prevalent multiple drug therapy, although the DCGI and Govt. of India do not favor more than 2 drugs in FDC combinations.<sup>14,15</sup>

Glimepiride is a common member of the SU family to be included in SP-FDCs for the treatment of people with T2DM. In fact, an earlier study reported PharmaTrac data of five top-selling SP-FDCs in India from November 2011 to October 2012, containing metformin. They were: (i) glimepiride/metformin, (ii) glimepiride/pioglitazone/metformin, (iii) glipizide/metformin, (iv) glibenclamide/metformin, and (v) gliclazide/metformin.<sup>3</sup> Another study assessed the different drug utilization patterns of metformin and demonstrated that among SP-FDCs containing metformin, metformin/glimepiride combination was prescribed highest by 59.5% (n=42). In studies by Sultana et al., Patel et al., and Brahmabhatt et al., the pre-dominance of metformin/glimepiride in the prescription pattern was also observed.<sup>16</sup> The beneficial effects of triple drug SP-FDC containing pioglitazone, the SU glibenclamide, and metformin on people with T2DM on insulin therapy was shown in a study by Panikar et al.<sup>17</sup>

In Table 1, the available SP-FDCs containing glimepiride, used in people with T2DM have been listed.

### Clinical Evidences on the Efficacy of SP-FDC Containing Glimepiride in T2DM Management

The START study by Devarajan et al. 2017 compared the safety and efficacy of glimepiride/metformin vs. sitagliptin/metformin combinations in people with T2DM for a period of 12 weeks. This randomized, open-label, comparative, multicenter study included 305 people with T2DM. Compared to sitagliptin/metformin combination, significant reduction in glycemic parameters were obtained in people receiving glimepiride/metformin combination.<sup>19</sup> A randomized, open-label study compared the glycemic controlling effects of metformin/glimepiride vs. metformin/glibenclamide combination in 31 participants for 12 weeks. The results of the study indicated significantly greater reductions in glycemic parameters for metformin/glimepiride combination.<sup>20</sup>

In a post marketing surveillance, noncomparative, mono-centric study, the efficacy and safety of triple SP-FDC containing glimepiride, voglibose, and metformin was assessed in 50 people with T2DM. This triple-combination SP-FDC was found to be effective in controlling HbA<sub>1c</sub>, fasting, and post prandial blood glucose.<sup>21</sup> In another study by Bell et al., the efficacy of triple SP-FDC, containing glimepiride, metformin, and pioglitazone, was compared with that of human insulin and sustained release metformin, in 101 insulin-naïve people with T2DM, for 12 weeks. The study revealed greater efficacy and tolerability of the triple SP-FDC than metformin and insulin.<sup>22</sup>

All these evidences indicate the potential role of glimepiride as a constituent of both dual and triple SP-FDC in the effective control of hyperglycemia in people with T2DM.

### Conclusion

Since T2DM is a progressive disease, monotherapy with metformin mostly fails to maintain long-term effective glycemic control. This necessitates the administration of second-line or even third-line therapeutic agents, as add-on to metformin therapy. SP-FDCs play

a very crucial role in the achievement of desired glycemic targets in people with T2DM. SP-FDCs are preferred over multi-pill combination therapies in people with diabetes mellitus. The efficacy and safety of glimepiride in SP-FDCs is well-validated, and hence is widely used.

#### Conflict of Interest

SM is an employee of Sanofi India. All other authors report no conflicts of interest.

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#### Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, reviewed and have given their approval for the final version to be published.

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