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Glimepiride+Metformin HCl

Solosamet ® SR

2 mg/500 mg Prolonged-Release Tablet

Oral Hypoglycemic Agent

sanofi

Product Description

White, oblong, biconvex, film-coated tablets, engraved with "SR25" on one side

Formulation

Each tablet contains:

Glimepiride ..... 2 mg

Metformin HCl ..... 500 mg

Indications

As an adjunct to diet and exercise in type 2 diabetes mellitus patients

- In case that the monotherapy with glimepiride or metformin does not result in adequate glycemic control
- Replacement of combination therapy of glimepiride and metformin

Dosage and Administration

General

In principle, the dosage of Glimepiride + Metformin HCl (Solosamet SR) is governed by the desired blood glucose level. The dosage of Glimepiride + Metformin HCl (Solosamet SR) must be the lowest which is sufficient to achieve the desired metabolic control.

During treatment with Glimepiride + Metformin HCl (Solosamet SR) glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determinations of the proportion of glycated haemoglobin be carried out.

Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose.

Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal) or situations where a dose cannot be taken at the prescribed time must be discussed and agreed between physician and patient beforehand.

As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glimepiride requirements may fall as treatment proceeds. To avoid hypoglycaemia timely dose reduction or cessation of Glimepiride + Metformin HCl (Solosamet SR) therapy must therefore be considered.

Glimepiride + Metformin HCl (Solosamet SR) should be administered once per day during breakfast or the first main meal.

The highest recommended dose per day should be 8 mg of glimepiride and 2000 mg of metformin. Daily doses of glimepiride of more than 6 mg are more effective only in a minority of patients.

In order to avoid hypoglycaemia the starting dose of Glimepiride + Metformin HCl (Solosamet SR) should not exceed the daily doses of glimepiride or metformin already being taken.

When switching from combination therapy of glimepiride plus metformin as separate tablets, Glimepiride + Metformin HCl (Solosamet SR) should be administered on the basis of dosage currently being taken.

Titration:

The daily dose should be titrated in increments of 1 tablet only, corresponding to the lowest strength (in case various strengths are available).

- Duration of treatment

Treatment with Glimepiride + Metformin HCl (Solosamet SR) is normally a long-term therapy.

Special Populations

Children

Data are insufficient to recommend pediatric use of Glimepiride + Metformin HCl (Solosamet SR).

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section Warnings) should be reviewed before considering initiation of metformin in patients with GFR<60 mL/min.If no adequate strength of Glimepiride + Metformin HCl (Solosamet SR) is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/ min	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see Section Warnings) should be reviewed before considering initiation of metformin.
30-44	1000 mg	The starting dose is at most half of the maximum dose.
<30	-	Metformin is contraindicated.

Administration

Due to the sustained release formulation, Glimepiride + Metformin HCl (Solosamet SR) must be swallowed whole and not crushed or chewed.

Contraindications

For Glimepiride:

- in patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, or any of the excipients of Glimepiride + Metformin HCl (Solosamet SR).
- in pregnant women.
- in breast-feeding women.

No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function and in dialysis patients. In patients with severe impairment of hepatic function, change-over to insulin is indicated, not least to achieve optimal metabolic control.

For Metformin:

- Hypersensitivity to metformin or any of the excipients.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma).
- Severe renal failure (GFR < 30 mL/min).
- Acute conditions with the potential to alter renal function such as:

- dehydration
- severe infection
- shock
- Intravascular administration of iodinated contrast agents (see section Warnings and section Precautions)

- Acute or chronic disease which may cause tissue hypoxia such as:

- cardiac or respiratory failure
- recent myocardial infarction
- shock

- Hepatic insufficiency.
- Acute alcohol intoxication, alcoholism.
- Lactation.

Warnings

For Glimepiride:

In exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

For Metformin:

- Lactic acidosis

Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients.

Other risk factors assoiated to lactic acidosis are excessive alcohol intake, hepatic isufficiency, inadequately controlled diabetes, ketosis, prolonged fasting, and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections Contraindications and Interactions).

Diagnosis:

Patients and/or care-givers should be informed of the risk of lactic acidosis. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH(<7.35), increased plasma lactate levels (> 5 mmol/L), and an increased anion gap and lactate/pyruvate ratio.

- Renal function

GFR should be assessed before treatment initiation and regularly thereafter (see Section Dosage and Administration). Metformin is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function, see Section Contraindications.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

- Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections Dosage and Administration and Interactions.

- Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Precautions

For Glimepiride

In the initial weeks of treatment, the risk of hypoglycaemia may be increased and necessitates especially careful monitoring.

Factors favouring hypoglycaemia include:

- unwillingness or (more commonly in older patients) incapacity of the patient to co-operate.
- undernourishment, irregular mealtimes or skipped meals.
- imbalance between physical exertion and carbohydrate intake.
- alterations of diet.
- consumption of alcohol, especially in combination with skipped meals.
- impaired renal function.
- severe impairment of liver function.
- overdosage with glimepiride.
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or corticoadrenal insufficiency).
- concurrent administration of certain other medicines (see under Section Interactions).
- treatment with glimepiride in the absence of any indication.

If such risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of glimepiride or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life-style changes.

Those symptoms of hypoglycaemia which reflect the body's adrenergic counter-regulation (see Section Adverse Reactions) may be milder or absent where hypoglycaemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic drugs.

Hypoglycaemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar).

It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation.Severe hypoglycaemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

For Metformin:

Renal function:

As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function,
- at least two to four times a year in patients with serum creatinine levels at the limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent:

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery:

Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see section Adverse Reactions).

Long-term treatment with metformin has been associated with a decrFe vitamin B12 level is recommended (see Section Adverse Reactions).

Other precautions:

- All patients should continue their diet with a regular distribution of carbohydrate intake duringthe day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas.

Interactions

For Glimepiride:

Based on experience with glimepiride and on what is known of other sulfonylureas, the following interactions must be considered:

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP 2C9.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

insulin and other, oral antidiabetics; ACE inhibitors; anabolic steroids and male sex hormones; chloramphenicol; coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine; fenyramidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; para-aminosalicylic acid; pentoxifylline (high dose parenteral); phenylbutazone; azapropazone; oxyphenbutazone; probenecid; quinolones; salicylates; sulfinpyrazone; clarithromycin; sulfonamide antibiotics; tetracyclines; tritoqualine; trofosfamide.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example: acetazolamide; barbiturates; corticosteroids; diazoxide; diuretics; epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (after protracted use); nicotinic acid (in high doses); oestrogens and progestogens; phenothiazines; phenytoin; rifampicin; thyroid hormones.

H2 receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of glimepiride in an unpredictable fashion.

The effect of coumarin derivatives may be potentiated or weakened.

Bile acid sequestrant: Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore glimepiride should be administered at least 4 hours prior to colesevelam.

For Metformin:

Concomitant use not recommended:

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition, or hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents

Metformin must be discontinued prior to, or at the time of the imaging procedure and not restarted until 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections Dosage and Administration and Warnings.)

Combinations requiring precautions for use:
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation. ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation. Metformin may decrease the anticoagulant effect of phenprocoumon. Therefore, a close monitoring of the INR is recommended.
Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated or stopped, and the dosage of metformin must be adjusted if necessary.

Pregnancy
For Glimepiride:
Glimepiride must not be taken during pregnancy. Otherwise there is risk of harm to the child. The patient must change over to insulin during pregnancy.
Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.
For Metformin:
To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development.
When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

Lactation
For Glimepiride:
To prevent possible ingestion with the breast milk and possible harm to the child, glimepiride must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.
For Metformin:
Metformin is excreted into milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

Driving a Vehicle or Performing Other Hazardous Tasks
For Glimepiride:
Alertness and reactions may be impaired due to hypo- or hyperglycaemia, especially when beginning or after altering treatment or when glimepiride is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.
For Metformin:
Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.
However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).

Adverse Reactions
The following CIOMS frequency rating is used, when applicable:
Very common ≥10%; Common ≥ 1 and <10%; Uncommon ≥ 0.1 and <1%; Rare ≥ 0.01 and <0.1%; Very rare <0.01%, Unknown (cannot be estimated from available data).
For Glimepiride and Metformin:
The use of a combination of both compounds, either as a free combination or as a fixed combination, is associated with the same safety characteristics as the use of each compound separately.
For Glimepiride:
• Metabolism and nutrition disorders
As a result of the blood-glucose-lowering action of glimepiride, hypoglycaemia may occur, which may also be prolonged.
Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, pareses, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia.
In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias. The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke.
The symptoms nearly always subside when hypoglycaemia is corrected.
• Eye disorders
Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependent on blood glucose level.
• Gastrointestinal disorders
Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur.
In isolated cases, there may be hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice, which may progress to life-threatening liver failure but can regress after withdrawal of glimepiride.
Dysgeusia (frequency not known).
• Blood and lymphatic system disorders
Changes in the blood picture may occur: Rarely, thrombocytopenia and, in isolated cases, leucopenia, haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop. Cases of severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura have been reported in post-marketing experience (frequency not known).
• Skin and subcutaneous tissue disorders
Alopecia (frequency not known)
• General disorders
Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Such mild reactions may develop into serious reactions with dyspnoea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must therefore be notified immediately.
In isolated cases, a decrease in serum sodium concentration and allergic vasculitis or hypersensitivity of the skin to light may occur.
• Investigations
Glimepiride, like all sulfonylureas, can cause weight gain (frequency not known)
For Metformin:
Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (>10%) are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.
- Metallic taste (3%) is common.
- Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (<0.01%).
- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%).
  However, cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in post-marketing experience (frequency not known) (see Section Precautions).
- Lactic acidosis (0.03 cases/1000 patient-years) is very rare (see Section Warnings).
- Hemolytic anemia (frequency unknown)
- Reduction of thyrotropin level in patients with hypothyroidism (see section Precautions) (frequency unknown)
- Hypomagnesemia in the context of diarrhea (frequency unknown)
- Encephalopathy (frequency unknown)
- Photosensitivity (frequency unknown)
- Hepatobiliary disorders: Reports of liver function tests abnormalities and hepatitis resolving upon metformin discontinuation.

Overdose
Signs and Symptoms
For Glimepiride:
Acute overdosage as well as long-term treatment with too high a dose of glimepiride may lead to severe life-threatening hypoglycaemia.
Management
As soon as an overdose of glimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose.
Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycaemia may recur after initial recovery.
Admission to hospital may sometimes be necessary even as a precautionary measure. In particular, significant overdoses and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital.
If, for example, the patient is unconscious, an intravenous injection of concentrated glucose solution is indicated (for adults starting with 40 ml of 20% solution, for example). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1 mg i.v., s.c. or i.m., may be considered.
In particular when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be very carefully adjusted in view of the possibility of producing dangerous hyperglycaemia, and must be controlled by close monitoring of blood glucose.
Patients who have ingested life-threatening amounts of glimepiride require detoxification (e.g. by gastric lavage and medicinal charcoal).
After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, hypoglycaemia, or the danger of slipping back into hypoglycaemia, may persist for several days.
For Metformin:
Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.Pancreatitis may occur in the context of a metformin overdose.

Pharmacodynamics
Clinical Efficacy/Clinical Studies
A 16-week, double-blind, double-dummy, two-arm, parallel group study was conducted to compare the efficacy and safety of glimepiride/metformin SR 2/500 mg daily (OD) versus glimepiride/metformin 1/250 mg twice daily (BID) in patients with type 2 diabetes mellitus (T2DM).10 Patients (N=207) were randomized to either glimepiride/metformin SR OD administered with the morning meal or glimepiride/metformin BID administered with the morning and evening meal. The primary objective was to
demonstrate equivalence, based on the mean change in glycated hemoglobin (HbA1c) from baseline to endpoint (week 16) between glimepiride/metformin SR 2/500 mg OD and glimepiride/metformin 1/250 mg BID.
HbA1c at baseline was 8.05% in glimepiride/metformin SR OD group and 8.13% in glimepiride/metformin BID group. At study end, HbA1c was decreased by 0.59% (adjusted mean = 0.61%) to a mean value of 7.47% for glimepiride/metformin SR OD and by 0.67% (adjusted mean = 0.65%) to 7.46% for glimepiride/metformin BID.
Difference in adjusted mean between the two treatment groups was 0.04% with (-0.16%, 0.24%) of its confidence interval. Therefore, 95% two-sided confidence interval for the difference in change of HbA1c existed within the equivalence range (-0.5%, +0.5%).
Regarding nocturnal hypoglycemia there was no significant difference between the two treatment groups.Likewise, statistical significance was not observed between treatment groups based on the frequency of hypoglycemia. No statistical significance was observed between the two groups with regard to adverse events, although the occurrence was lower in the glimepiride/metformin SR OD treatment group.

Pharmacokinetics
Glimepiride pharmacokinetics (Tmax and AUC) after meal was similar between a sustained-release formulation of Glimepiride + Metformin HCl (Solosamet SR) 2/500 mg and an immediate-release formulation of single Glimepiride + Metformin HCl (Solosamet) 2/500 mg or BID. Glimepiride + Metformin HCl (Solosamet) 1/250 mg. Meanwhile, metformin tmax was delayed in sustained-release formulation compared to immediate-release formulation, but its elimination half-life was not prolonged.
The extent of metformin exposure after meal was lower in sustained-release formulation than in immediate-release formulation and its B.I.D. treatment in divided doses by 14% and 23% on average respectively. This effect on exposure is not considered clinically significant as there was no significant difference in safety between treatment groups.

An open label, 3-period, 3-treatment, 3-way crossover study was conducted in 12 healthy Korean male subjects to evaluate the pharmacokinetic and safety profiles of Glimepiride + Metformin HCl (Solosamet) and Glimepiride + Metformin HCl (Solosamet SR) tablets. Subjects were randomized to one of 3 treatment arms (Group A, B or C). Subjects in group A received a single Glimepiride + Metformin HCl (Solosamet SR) 2/500 mg after breakfast. Group B received a single Glimepiride + Metformin HCl (Solosamet) 2/500 mg after breakfast. Group C received Glimepiride + Metformin HCl (Solosamet) 1/250 mg after breakfast and 12 hours later after dinner. There was a 7-day washout period between each treatment period.

Pharmacokinetic parameters

	(Glimepiride + Metformin HCl) Solosamet SR 2/500		(Glimepiride + Metformin HCl) Solosamet 2/500		Glimepiride + Metformin HCl) Solosamet 1/250			
	Glimepiride	Metformin	Glimepiride	Metformin	Glimepiride		Metformin	
	AM dose	AM dose	AM dose	AM dose	AM dose	PM dose	AM dose	PM dose
t_{max} (h)	4.0 [2.0 -5.0]	5.0 [4.0 -8.0]	3.5 [2.6 -8.0]	3.5 [2.0 -4.0]	3.5 [1.5 - 4.0]	5.0 [1.0 -8.0]	4.0 [1.0 -4.0]	4.0 [2.0- 6.0]
C_{max}	179.6 ± 46.5	586.5 ± 153.6	179.6 ± 56.0	861.3 ± 177	93.0 ± 35	58.8 ± 13.8	504.5 ± 136.8	510.2 ± 124.4
AUC_{24}	793.2 ± 206.0	5328.2 ± 1397.8	752.3 ± 180.6	6181.7 ± 1313.7	730.5 ± 184.1		6952.0 ± 1697.0	
$t_{1/2}$ (h)	9.2	5.7	8.2	5.5	3.0		3.1	

Values are presented as mean ± SD except Tmax : median [min – max]

Storage
Store at temperatures not exceeding 30°C. Protect from humidity.

Caution
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Availability
Box of 30's (Aluminum/PVC/PVDC/PE Blister Pack x 10's)

Reporting of side effects or any suspected adverse event
For suspected adverse drug reaction, report to the FDA : **www.fda.gov.ph.**
If you experience any side effects after taking/having the product, you are advised to seek medical attention.
You are also encouraged to report any side effects to Sanofi Philippines Pharmacovigilance Unit via email at **PV.Philippines@sanofi.com.** By reporting side effects, you can help provide more information on the safety of the product.

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