

**GlyMet      F.C.    Tablets**

(Film coated tablet of Glibenclamide and Metformin HCl)    Used under prescription only

**[ Active Ingredients ]**

**GLYMET F.C. TABLETS 5/500MG** Each tablet contains Metformin hydrochloride 500 mg and Glibenclamide 5 mg.

**[ Features ]**

**GLYMET F.C. TABLETS 5/500MG** Yellow-colour biconvex, oblong film-coated tablets, with the trademark ‘e’ on one side and a score line & ‘03’ on the other side.

**[ Indications ]**

GLYMET is indicated as initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.

GLYMET is indicated as second-line therapy when diet, exercise, and initial treatment with a sulfonylurea or metformin not result in adequate glycemic control in patient with type 2 diabetes.

**[ Dosage ]**

Oral and used for adults only. This drug has to be used under prescription only.

**General Considerations:**

Dosage of GLYMET must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20 mg glibenclamide/2000 mg metformin.

GLYMET should be given with meals and should be initiated at a low dose with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glibenclamide), to reduce GI side effects (largely due to metformin), and to permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response of GLYMET and to identify the minimum effective dose for the patient. Thereafter, HbA1c should be measured at intervals of approximately 3 months to assess the effectiveness of therapy.

**1.    GLYMET as Initial Therapy**

Recommended starting dose: 250/1.25 mg once or twice daily with meals.

For patient with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of GLYMET is 250/1.25 mg once a day with a meal.

As initial therapy in patient with baseline HbA1c > 9% or an FPG > 200 mg/dl, a starting dose of GLYMET 250/1.25 mg twice daily with the morning and evening meals may be used. Dosage increase, should be made in increments of 250/1.25 mg per day every two weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose.

There was no experience with total daily doses greater than 10 mg/2000 mg per day.

**GLYMET 500/5 mg should not be used as initial therapy due to an increased risk of hypoglycemia.**

**2.    GLYMET Used in Previously Treated Patients (Second line Therapy)**

Recommended starting dose: 500/2.5 mg or 500/5 mg twice daily with meals.

For patient not adequately controlled on either glibenclamide (or another sulfonylurea) or metformin alone, the recommended starting dose of GLYMET is 500/2.5 mg or 500/5 mg twice daily with the morning and evening meals.

In order to avoid hypoglycemia the starting dose of GLYMET should not exceed the daily doses of glibenclamide or metformin already being taken.

The daily dose should be titrated in increments of no more than 500/5 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.

For patients previously treated with combination therapy of glibenclamide (or another sulfonylurea) plus metformin, if switched to GLYMET, the starting dose should not exceed the daily dose of glibenclamide (or equivalent dose of another sulfonylurea) and metformin already being taken.

Patient should be monitored closely for signs and symptoms of hypoglycemia following such as a switch and the dose of GLYMET should be titrated as described above to achieve adequate control of blood glucose.

**Specific Patient Populations**

GLYMET is not recommended for use during pregnancy or for use in pediatric patients.

The initial and maintenance dosing of GLYMET should be conservative in patients with advanced age, due to the potential for decreased renal function in this population.

Any dosage adjustment requires a careful assessment of renal function.

Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of GLYMET to avoid the risk of hypoglycemia.

Monitoring of renal function is necessary to aid of metformin-associated lactic acidosis, particularly in the elderly.

**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 should be reviewed before considering initiation of metformin in patients with GFR <60 ml/min.

If no adequate strength of Glymet is available, individual monocomponents should be used instead of the fixed dose combination.

| GFR<br>mL/min | Metformin                                                                                                | Glibenclamide                    |
|---------------|----------------------------------------------------------------------------------------------------------|----------------------------------|
| 60-89         | Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function. | -                                |
| 45-59         | Maximum daily dose is 2000 mg.<br>The starting dose is at most half of the maximum dose.                 | -                                |
| 30-44         | Maximum daily dose is 1000 mg.<br>The starting dose is at most half of the maximum dose.                 | -                                |
| <30           | Metformin is contraindicated.                                                                            | Glibenclamide is contraindicated |

Contraindication for use:

For the patients included in the following cases, it is not allowed to take this drug:

- The one is allergic to metformin hydrochloride, glibenclamide, a drug in the category of sulfonylurea and sulfonamide, or any kind of an excipient.
- Type 1 diabetes (Insulin dependent diabetes), diabetic ketoacidosis (DKA) and diabetic pre-coma.
- Renal failure or renal dysfunctional (i.e. the creatinine value in serum of a man > 135 µmol/L, and the creatinine value in serum of a woman > 110µmol/L).
- Having potential acute symptoms to change the renal function, e.g. dehydration, severe infection, shock and iv administration of Iodinated contrast media. (Please see “Warnings and precaution”)
- Hypoxemia resulted from an acute or chronic disease. e.g. cardiac or respiratory failure, recent myocardial infarction and shock.
- Hepatic failure, acute alcoholism and a heavy drinker.
- Porphyria
- In the period of lactation
- A combined use with drugs of miconazole (Please see “Drug interactions”)
- Severely reduced kidney function (GFR <30 mL/min)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

**[ Warning and precaution ]**

**Lactic acidosis:**

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. 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 for lactic acidosis are excessive alcohol intake, hepatic insufficiency, 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.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. 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.

Lactic acidosis is a rare but severe metabolic complication (with a high death rate if it is not treated on time) that is resulted from the accumulation of metformin in a body. In reported cases that patients had lactic acidosis after using metformin, the main cause was that diabetic patients had already had remarkable renal failure. If a patient is having other relative hazardous factors like the uncontrolled blood sugar of a diabetic patient, ketosis, a long-term fast, a heavy drinker, hepatic dysfunction and situations related to hypoxemia, it is better that the patient can avoid to use metformin after evaluation to lower the incidence rate of lactic acidosis.

**Diagnosis**

The manifested features include acidosis dyspnea, abdominal pain, hypothermia and the following coma. The present diagnostic inspection values include the lowered pH value of blood, the lactic acid value in plasma higher than 5 mmol/L, the increased anion gap and the bigger lactate/pyruvate ratio. If there is a doubt about the metabolic acidosis coming to a patient, it is necessary to stop the drug immediately and go for treatment. (Please see “Overdosed use”)

**Hypoglycemia**

Because GlyMet contains some component of sulfonylurea, a patient taking it has to face the risk of hypoglycemia. This therapy is only given to the patients having their meals (including breakfast) regularly. The risk of hypoglycemia will increase with the delayed dietary time, insufficient diet or the imbalanced carbohydrates. Therefore, it is important to regularly have carbohydrates. For the patients limited to control their calories, hypoglycemia will probably come to them after heavy or long-term exercise, as drinking or during the use of the combination with hypoglycemic drugs.

**Diagnosis**

The manifested features include headache, hunger, nauseating, vomiting, the feel of extreme fatigue, improper sleep, feeling ill at ease, aggressiveness, worse attention and response, psychical disorderliness, inarticulacy, disturbed vision, trembling, paralysis and abnormal feeling, vertigo, delirious forgetting, convulsion, sleeping with weakness, unconsciousness, light breath and slow heart beating. Due to the negative regulation caused from hypoglycemia, a patient may have situations as sweating, fear, too fast heart beating, hypertension, palpitations, angina pectoris and arrhythmia. When hypoglycemia becomes obvious, a diabetic patient will not have symptoms described before if he has autonomic neuropathy or he is currently taking β-blockers, Clonidine, Reserpine, Guanethidine or other sympathomimetic agents.

**Treatment for hypoglycemia**

For a patient meeting the moderate level of hypoglycemia but still have consciousness or no neuropathy, the immediate sugar supplement might improve the symptom of hypoglycemia. The dose adjustment and 90r) the change of dietary method should be assured. It is possible to see a coma, occurrence of epilepsy or neurologically severe response of hypoglycemia, each of which is a medical emergency. If the cause has been figured out or been suspected, it is necessary to give an iv injection of glucose to the patient for treatment before entering a hospital. To avoid the occurrence of hypoglycemia is important to consider the patient and dosage and to give the patient proper health lessons.

**Factors that cause hypoglycemia easily**

- When combined with alcohol, especially in fast.
- The patient reject or unable to operate in coordination (especially for senile people)
- Malnutrition, irregular diet, wrong meal, fast or some change in diet.
- There is an imbalance between exercises and ingestion of carbohydrates.
- Renal failure
- Severe hepatic failure
- Overdose of GlyMet
- Endocrine disruption in some parts: Hypothyroidism, hypophysis and adrenal gland dysfunctions
- Combination with some drugs (Please see “Drug Interactions”)

**Renal function**

GFR should be assessed before treatment initiation and regularly thereafter [See Section Recommended Dosage]. 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].

**Renal and hepatic failure**

For the diabetic patients having hepatic failure and severe renal failure, the pharmacokinetics and (or) pharmacodynamics of GlyMet in their bodies might vary. Hypoglycemia may last for a long time if it is met in those patients, so the therapies for them should be adjusted properly.

**Suggestion for patients**

The danger, symptom, and therapy and the situation of being easily infected of hypoglycemia have to be exactly explained to a patient and his family members. Similarly, if there are nonspecific symptoms like muscle convulsion combined with uncomfortableness of stomach or intestine, abnormal pain, severe weakness, difficult breathing resulted from acidosis, hypothermia and coma, it is necessarily to think about the possibility of lactic acidosis. Especially, it is necessary to tell a patient the importance of a fixed diet and the regular measurement of blood sugar after exercises.

**Imbalance of blood sugar**

If a patient has undergoes a surgical operation or there is one of factors to make glycosuria without compensation in his body, it is necessarily to temporarily take insulin therapy instead of this drug. The symptoms of hyperglycemia include the increased quantity of urine, extreme thirsty and the dry skin.

**Renal function**

Metformin is excreted by kidney. The level of creatinine value in serum should be measured before the treatment and in the following regular treatment:

- For the patient having normal renal function: At least one time of measurement should be carried out per year.

For the patient having his level of creatinine value in serum locating in the maximum value of normal range and senile patients: At least 2-4 times of measurement should be carried out per year.

That a senile patient loses his renal function is quite common and not showing any symptom. In some cases like the use of anti-hypertension drugs or diuretics and the early stage of a therapy of using NSAIDs for analgesia, the patients shall have the insufficient renal function, so high level of care is required to treat them.

**Administration of iodinated contrast media**

In a radioactivity test, an iv injection of iodinated contrast media will lead to renal failure. It is necessary to stop the administration of this drug before the test, during the test and within 48 hr after the test. It is allowed to readminister this drug only after the evaluation that indicates the renal function has returned to a normal level. (Please see “Drug interactions”)

**Surgical operation**

Because GLYMET contains metformin hydrochloride, it is necessary to stop the administration of this drug 48 hr prior a general anesthetic operation; it is allowed to go back to the use of this drug only after 48 hr posterior to the operation.

## Other items or preventions

### SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

### Hypoxic states

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia.

When such events occur in patients on GLYM ET therapy, the drug should be promptly discontinued.

### Alcohol intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism.

Patient, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLYMET.

Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

- Because this drug contains lactose that has congenital galactosemia, poor absorption of glucose and galactose or insufficiency of lactase is prohibited from taking this drug

### 【 Drug interactions 】

#### GLYMET

- Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid product, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

- Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs as salicylates, sulfonamides, chloramphenicol, and probenecid as compared to sulfonylureas, which are extensively bound to serum proteins.

### Glibenclamide

- The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents.

- A possible interaction between glibenclamide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of hypoglycemic action of glibenclamide.

The mechanism for this interaction is not known.

-A potential interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

### Metformin Hydrochloride

- Furosemide

Pharmacokinetic parameters of both compounds were affected by co-administration.

- Nifedipine

Co-administration of nifedipine increased plasma metformin Cmax, and AUC and increased the amount excreted in the urine.

Nifedipine appears to enhance the absorption of metformin.

- Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport system.

### 【 Pregnancy and lactation 】

Recent information strongly suggests the abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities.

Most experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible.

Because animal reproduction studies are not always predictive of human response, GLYMET should not be used during pregnancy unless clearly needed.

Although it is not known whether glibenclamide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk.

Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue GLTMET, taking into account the importance of the drug to the mother.

### 【 Effects on driving and the operation of a machine 】

A patient should watch out the occurrence of hypoglycemia, and he or she is suggested to be careful when driving or operating a machine.

### 【 Side effects 】

Related to metformin:

- The symptoms of Stomach and intestine: The most common cases include nausea, vomiting, diarrhea, abdominal pain and poor appetite (>10%), which happen in the highest frequency. In the early stage of treatment and after the treatment, most of them disappear automatically. To avoid these side effects, the administration of daily dosage for 2-3 times is suggested. A slow augment of dosage may also improve the tolerance of stomach and intestine.

- Taste of metal (3%) is quite common.

- Some patients with hypertension have the syndrome of slight erythema. The incidence rate is quite low (<0.01%).

- It is observed from those patients taking long-term therapies of metformin that their vitamin B12 absorption is diminished and the concentration in serum is attenuated, but these issues are not clinically meaningful (<0.01%).

- Lactic acidosis (3 individual cases from 100,000 patients per year) is quite rare. (Please see "Warnings and precaution")

Related to glibenclamide:

- Hypoglycemia. (Please see "Warnings and precaution")

- Responses of skin and mucous membrane: Itching, urticaria and maculopapular eruptions. There were photosensitive reactions seen in few cases. There were shock reactions seen in very few cases of urticaria. It was rare that allergic vasculitis observed on skin and in viscera.

Allergic vasculitis rarely became maculopapular eruptions with diversity and exfoliative dermatitis. Cross-interaction might be seen between sulfonamide and its derivatives.

- For the discomfort of stomach and intestine: Nausea, diarrhea and the pressed upper quadrant.

- For liver: An individual that has an augment of hepatic enzymes and the hepatitis probable to have lytic activity or cholestasis should cease the therapy of this drug.

- After the cease of drugs, symptoms of problems about blood will return: Reduced white blood cells and decreased platelets. Rare cases: Agranulocytopenia, hemolytic anemia,

myelodysplastic syndromes and diminished complete blood cells.

- There are risks of hepatic porphyria and dermal porphyria cutanes.

- Isolated cases of hyponatremia.

- Other abnormal values of experimental inspections: Occasionally, values of urine in blood and creatinine equalize to moderate and increase.

- A withdrawal reaction like disulfiram may appear as combined with ethanol.

- In the early stage of treatment, some temporary visual obstruction may be resulted from the lowered blood sugar.

### 【 Overdose 】

#### Glibenclamide

Overdosage of sulfonylureas, including glibenclamide tablets, can produce hypoglycemia.

Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization.

If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution.

This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

#### Metformin Hydrochloride

Hypoglycemia has not been seen even with ingestion of up to 85 grams of metformin hydrochloride, although lactic acidosis has occurred in such circumstances.

Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions.

Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

## 【 Pharmacological properties 】

### 【 Pharmacodynamics 】

Class of the pharmacological treatment: The combined therapy of biguanide with sulfonamides. Metformin is a kind of biguanide to lower blood sugar level by lowering both basic blood sugar level and the blood sugar level after meal. Without the stimulation to secrete insulin and choline, no hypoglycemia will occur.

The effect of metformin is built up through 3 mechanisms:

1) Reduce the generation of hepatic glucose by inhibiting gluconeogenesis and glycogenolysis.

2) Increase the sensitivity of muscle tissues to insulin and promote the absorption and use of glucose in peripheral tissues.

3) Delay the absorption of glucose in an intestine.

Metformin has the effect on glycogen synthases to stimulate the intracellular glycogen synthesis. Metformin can increase the delivering ability of every membrane glucosetransport unit (GLUT). For a human body, metformin can not only reduce blood sugar level but also help lipid metabolism. It is indicated in mid- and long-term clinical trials: metformin can diminish levels of total cholesterol, low density lipid protein cholesterol and triglyceride. Until now, it has not been shown in clinical trials that a drug combination therapy of metformin and glibenclamide can lower the lipid metabolism.

Glibenclamide is a sulfonylurea of the second generation with a moderate half life: It is able to stimulate the pancreas to release insulin, which leads to acute hypoglycemia. This effect is performed in accordance with the existence of functional  $\beta$  cells in Islet of Langerhans. It is very important that glibenclamide stimulates the secretion of insulin to respond to feeding.

After the administration of glibenclamide in a diabetic patient, an insulin response after meal will be amplified. After a drug therapy for at least 6 months, responses of the insulin after meal and the increased secretion of C-peptide will still continue.

Metformin and glibenclamide have different mechanisms and targets, but their effects are complementary to each other. glibenclamide stimulates the pancreas to secrete insulin while metformin is working in peripheral skeletal muscles to reduce the cellular resistance for insulin and the sensitivity of hepatic cells.

For the Type II diabetic patients that still do not receive a blood sugar control after their diets and exercises combined with a single drug therapy of either metformin or glibenclamide, it has been proven that there is a synergic effect from combined drugs on the regulation of glucose after finishing trials of the control, double blind and comparison of this drug.

### 【 Pharmacokinetics 】

#### Related to the compound prescription drug of GlyMet

The bioavailability of the administration of the compound prescription drug composed of metformin and glibenclamide is similar to that of both administrations of 1 tablet metformin plus 1 tablet glibenclamide. In the compound prescription drug, the bioavailability of metformin is not affected in the presence of food. In the compound prescription drug, the bioavailability of glibenclamide is not affected in the presence of food either, but feeding can increase the absorption rate for it.

#### Related to metformin

Absorption: After oral administration of single dosage of metformin, Tmax of the concentration in blood will be achieved by 2.5 hr. Oral administration of one tablet of glucophage 500mg or 850 mg in a healthy subject's body leads to an absolute bioavailability of nearly 50%-60%. After oral administration of one dosage, the unabsorbed drug cleared from stool is 20-30%. After oral administration, the absorption of metformin is saturated and incomplete. The pharmacokinetics of absorbed metformin is nonlinear. In common metformin dosage and dose administrating time, a stable concentration in blood can be achieved by 24-28 hr and is generally lower than 1 ug/mL. In the clinical trials with controls, even the highest doses were given, but Cmax of metformin in plasma was still lower than 4 ug/mL.

Distribution: The binding with a serum protein is negligible. Metformin will enter red blood cells, whereas Cmax in complete blood is lower than that in serum, but the time points they achieved are similar. It seems like that red blood cells are the second distribution place. The mean distribution volume (Vd) is 63-276 L.

Metabolism: Metformin is excreted in its original form in urine. There is not any metabolite found in a human body.

Clearance: Renal clearing rate of metformin is higher than 400 ml/min, which indicates is filtered through glomerulus and secreted by renal tubules, and then excreted. After oral administration of one dose, it is obvious that the terminal excreting half life is nearly 6.5 hr. When renal function is diminished, renal clearing rate is lowering in proportion to the decrease of creatinine; thus, excreting half life will be elongated, which will lead to an increase of metformin level in plasma.

#### Related to glibenclamide

Absorption: Glibenclamide will be easily absorbed after oral administration (>95%), whereas Cmax in blood can be achieved by 4 hr.

Distribution: Glibenclamide can greatly bind with plasma proteins, which may lead to some drug interactions.

Metabolism: Glibenclamide can be completely metabolized into 2 kinds of metabolites in liver. Hepatic cell failure results in the decrease of the metabolism of glibenclamide and the slow excretion.

Excretion: Glibenclamide will be completely evolved out within 45-72 hr in a form of metabolite through the excretion of biliary tract system (60%) and urine (40%).

The terminal excreting half life is nearly 4-11 hr. If renal dysfunction is met, to the excretion of metabolites in biliary tract will be improved as the clearing rate of creatinine is up to 30 mL/min based on the severity of renal damage. If the clearing rate of creatinine is still maintained above 30mL/min, the clearance of glibenclamide will not be affected by renal dysfunction.

### 【 Preclinical safety data 】

There are no relative preclinical safety data. According to the result of general studies in which metformin and glibenclamide were repeatedly tested for potential possibilities of dosage toxicity, genetic toxicity and carcinogenicity, metformin and glibenclamide do not have any special danger to a human body in preclinical assessments. In animal studies of metformin and glibenclamide, it is not shown that they will directly or indirectly hurt the pregnancy, the development of an embryo / fetus and the perinatal development of a fetus. (Please see "Pregnant women and the lactation period")

### 【 Storage 】

Store below 30°C.

### 【 Expiration date 】 : Three years

### 【 Packaging 】 :

Blister of 56s/box

Blister of 112s/box

Manufacturing Plant: Orient Pharma Co., Ltd.

Manufacturing Plant address: No. 8 Kehu 1st Rd., Huwei Township, Yunlin County 632, Taiwan, R.O.C.

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