VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Diabetes mellitus is a metabolic disease characterised by increased levels of blood sugar. If the human body is incapable of producing insulin properly, the patient is suffering from Type 1 diabetes mellitus (T1DM), also known as insulin-dependent diabetes mellitus. These patients have to inject insulin. If, in contrast, the body acquires insulin resistance, meaning, the body cells lose their ability to absorb and process insulin correctly, the patient is suffering from Type 2 diabetes mellitus (T2DM).

The prevalence in economically developed countries is estimated to be 15-20%.Obesity is thought to be the main cause of T2DM, and the risk of T2DM increases with age. Due to the demographic change, the globally proceeding industrialisation, urbanisation and the simultaneously decreasing physical activity of humans, the prevalence of T2DM is increasing worldwide.

Countries with a high prevalence of T2DM are Saudi Arabia, the USA and Switzerland, whereas countries with low prevalence are China and Iceland. It is assumed that in 2030, the number of patients with T2DM will have doubled in China. While the number of diabetic patients was about 171 million worldwide in 2000, forecasts for 2030 assume that 366 million patients will be affected.

VI.2.2 Summary of treatment benefits

Gliclazide is a hypoglycaemic sulfonylurea oral antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.
Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.
In addition to these metabolic properties, gliclazide has haemovascular properties.

Effects on insulin release
In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose.

Haemovascular properties
Gliclazide decreases microthrombosis, which may be involved in complications of diabetes, by two mechanisms:
- a partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B_2).
- an action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

VI.2.3 Unknowns relating to treatment benefits

There is no experience with the use of gliclazide during pregnancy in humans, even though there are few data with other substances from the same therapeutic class. It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, the product is contra-indicated in breast-feeding mothers.

The safety and efficacy of Gliclazide 30mg Modified release tablets in children and adolescents have not been established. No data are available in children.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Coma due to too low blood sugar (Diabetic pre-coma and coma, diabetic keto-acidosis))	Do not take [Product Name] if you have ketone bodies and sugar in your urine (this may mean you have diabetic keto-acidosis), a diabetic pre-coma or coma Gliclazide should only be taken if you have regular food intake otherwise you may develop a low blood sugar up to coma . You can experience too low blood sugar when you e.g. – take too much exercise without eating an adequate amount of carbohydrates – skip meals or have irregular meals – have kidney or liver insufficiency – accidentally overdose on gliclazide tablets	During Gliclazide treatment regular monitoring of your blood (and possibly urine) sugar levels and also your glycated haemoglobin (hbA1c) is necessary. In the first few weeks of treatment the risk of having reducing blood sugar levels (hypoglycaemia) may be increased. So close monitoring is necessary. Be aware of symptoms of a low blood sugar level (hypoglycaemia) including sweating, shaking, paleness, hunger, headache, irregular or fast heart beat, blurred vision, irritability, forgetfulness and confusion. To prevent coma, in most cases of low blood sugar levels, symptoms will resolve if you consume sugar in a drink or food.
Allergic reactions (Hypersensitivity)	Allergic reactions to gliclazide, any other medicines of the same group (sulphonylureas or sulphonamides) or other ingredients are possible.	Do not take [PRODUCT NAME] 60 mg modified release tablets: if you are allergic to gliclazide or any of the other ingredients of this medicine (see Package Leaflet) or to any other medicines of the same group (sulphonylureas or sulphonamides).

Insulin-dependent diabetes (Type 1 diabetes)	[PRODUCT NAME] 60 mg modified release tablets is used to keep blood sugar at the correct level in adults with diabetes when it is not controlled by dietary measures, physical exercise and weight loss alone. Gliclazide is not effective in insulin-dependent diabetes.	Do not take [PRODUCT NAME] 60 mg modified release tablets: if you have insulin-dependent (Type 1) diabetes
Severe kidney or liver disease (Severe renal or hepatic insufficiency)	Gliclazide is mainly metabolised in the liver and excreted in the urine. Severe kidney or liver disease can result in an increased risk of developing adverse drug reactions.	Do not take [PRODUCT NAME] 60 mg modified release tablets: if you have severe kidney or liver disease
Increase in blood glucose levels following concomitant use of danazol, chlorpromazine, glucocorticoids, ritodrine, salbutamol, terbutaline (i.v.)	The blood glucose lowering effect of gliclazide may be weakened and raised blood sugar levels may occur when one of the mentioned medicines is taken.	Consult your doctor before you start taking another medicine. If you go into hospital tell the medical staff you are taking [PRODUCT NAME] 60 mg modified release tablets.
Increased risk of hypoglycaemia following concomitant use of gliclazide with miconazole , phenylbutazone, alcohol, other antidiabetic medicinal products (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), betablockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, Mono amine oxidase inhibitors (MAOIs), sulfonamides, clarithromycin and nonsteroidal anti-inflammatory drugs	The blood sugar lowering effect of gliclazide may be strengthened and signs of low blood sugar levels may occur when one of the mentioned medicines is taken.	Consult your doctor before you start taking another medicine. If you go into hospital tell the medical staff you are taking [PRODUCT NAME] 60 mg modified release tablets.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Cardiovascular events	Researchers found an association between intake of anti-diabetic drugs from the sulphonylurea class and the risk of cardiovascular diseases such as congestive heart failure. As gliclazide was evaluated alongside with other second class sulphonylureas, it is not possible to determine the solitary effect of gliclazide. The risk is closely monitored by the MAH.
Asthenia	Single cases in patients taking gliclazide were reported. A causal relationship to gliclazide cannot clearly be established. The risk is closely monitored by the MAH.
Cancer	Single cases of cancer in patients taking gliclazide were reported. A causal relationship to gliclazide cannot clearly be established. The risk is closely monitored by the MAH.
Risk of haemolytic anaemia in patients with G6PD-deficiency	Lowering of the haemoglobin level and breakdown of red blood cells (haemolytic anaemia) can occur in patients missing the enzyme glucose-6-phosphate dehydrogenase. If you know you have a family history of glucose-6-phosphate dehydrogenase deficiency or if you know you suffer from this condition, you should talk to your doctor before taking gliclazide tablets.
Concomitant use of gliclazide with anticoagulant therapy (warfarin)	Gliclazide may increase the effects of medicines used to reduce blood clotting (warfarin). Adjustment of the anticoagulant (warfarin) may be necessary.

Important missing information

Risk	What is known
Use in pregnancy	There is no experience with the use of gliclazide during pregnancy in humans, even though there are few data with other sulphonylureas. Gliclazide is not recommended for use during pregnancy.
Use in children	The safety and efficacy of Gliclazide 30mg Modified release tablets in children and adolescents have not been established.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay

language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation studies have been imposed or are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.