RACGP

RACGP National Faculty of Specific Interests

Submission for Stage Three of the Review for Medicines Used in the Treatment of Type 2 Diabetes

PBS Post-Market Review of Products Used in the Management of Diabetes

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PRELUDE

Background & Justification

The Australian Government's post-market monitoring program aims to ensure the continued safe, cost effective and quality use of medicines listed on the Pharmaceutical Benefits Scheme (PBS).

Based on self-reported data from the 2007-2008 National Health Survey, the prevalence of diabetes in Australia has increased from 407,900 in 1995 to 818,200. This substantial increase has been attributed to more people developing the disease, but also people with diabetes living longer and improved detection of the disease.

In 2012, the Drug Utilisation Sub-committee requested, and the Pharmaceutical Benefits Advisory Committee (PBAC) agreed to a complete review of diabetes medicines due to the considerable recent changes in diabetes management, including the PBS listing of a number of new anti-diabetic drugs. From this, a broader review is being developed which will encompass other aspects of diabetes management, including medicines used in the management of type 2 diabetes, blood glucose test strips and insulin pumps subsidised for use in juveniles with type 1 diabetes from low income families.

The Pharmaceutical Benefits Scheme's "Post Market Review of Products Used in the Management of Diabetes" identifies the purpose of this review as follows:

Appropriate medication and treatment management is a significant National Medicines Policy (NMP) issue and the Department of Health and Ageing will work with key partners to improve the management of diabetes in Australia, including a focus on medicines, devices and the delivery of support services to consumers. The objective of this review is to systematically evaluate the body of clinical evidence regarding diabetes interventions to ensure the most appropriate management of diabetes in clinical practice. This review aims to ensure that patients are using the most appropriate medicines and products, effectively, and safely, to achieve optimal health outcomes and support quality use of medicines.

- Current experiences with type 2 Diabetes medicines in terms of their health outcomes, efficacy, safety, particular combinations of medicines used, satisfaction with treatment, and other insights into drug management;

- Whether prescribers and consumers consider these medicines are used effectively, including benefit and cost; and

- Any information about preferred medicines for specific sub-populations of patients with type 2 Diabetes

OUR RESPONSE

The RACGP supports the process of review of the Pharmaceutical Benefits Scheme in provision of subsidized medication for people living with type 2 diabetes in Australia. It supports a transparent and robust evidence based process that acknowledges and incorporates improvement in the process of guidelines for the establishment of access and review of any such medication. It acknowledges the burden of morbidity and mortality that people living with type 2 diabetes are predisposed to, and accepts that improvements in general practice management of type 2 diabetes will ultimately contribute to reduction of these risks. It does advocate for the timely access for general practice to both current and newly emerging and efficacious evidence based diabetes therapies in a sustainable way.

We acknowledge that quality use of diabetes specific medicines in general practice will contribute to these improvements and acknowledges considerable burden of illness relates to the use of pharmaceutical agents, including but not limited to cost of medicines, side-effects of medications, complications arising from use of/or lack of use of any such agents. The greatest burden of disease for people with type 2 diabetes remains cardiovascular death combined with microvascular complications including eye, nerve and renal disease.

It is acknowledged that diabetes requires a "patient-centred" hierarchy of approaches in addition to glycaemic control.[2] These may include individually appropriate management of risks associated with any concomitant hypertension and dyslipidaemia. This is an additional burden for patients living with and managing their illness. Once complications arise the burden escalates for people living with diabetes. [5]

Introduction of new and novel agents anti-hyperglycemic agents have tried to address this burden of disease, by addressing surrogate goals such as efficacy of HB A1C lowering, with additional benefits such as lowered hypoglycaemic risks, weight neutral or weight losing effects, compared to previously available agents (sulphonylureas and insulin). However the long-term outcomes on cardiovascular risk reduction of either second generation sulphonylurea agents, and newer agents such as gliptins and GLP1 agonists, remains as a whole, yet undetermined, at this point in time.

We emphasise the need for closer consultation with the general practice profession through the RACGP in the implementation and reviews of any diabetes related prescribing algorithms within the Pharmaceutical Benefits Scheme. We also acknowledge the future need to allow clinicians access to emerging therapies that will improve the lives of people living with diabetes.

With this basis, the RACGP National Faculty of Specific Interests (NFSI) Diabetes Network wishes to discuss the following issues as addressed in the PBAC review:

Within general practice in Australia there are levels of guidelines to assist the implementation of appropriate quality use of Medicines when managing type 2 diabetes

Efficacy Guidelines
TGA approval information
NHMRC 2009 Guidelines [1]

Therapeutic Goals (Type 2 diabetes specific)
NHMRC 2009 Guidelines [1]
ADS [2]

Prescribing Guidelines
Diabetes Australia 2012/13 [3]
RACGP- Diabetes Australia Management in general practice guidelines 2011/12 [4]
National Prescribing Service documentation

As an outcome from these various evidence-based guidelines, different algorithms for general practice have developed that incorporate references to the Pharmaceutical Benefits Scheme. Thus it should be acknowledged that such algorithms assume the cost-benefit analysis of the current PBAC approval and review process is incorporated in published PBAC recommendations.

SPECIFIC PATIENT GROUPS THAT NEED CONSIDERATION IN THIS REVIEW

A) "NEWLY" DIAGNOSED TYPE 2 DIABETES VERSUS B) TYPE 2 DIABETES WITH ESTABLISHED CARDIOVASCULAR DISEASE OR HIGH CARDIOVASCULAR RISK

A) **"NEWLY" DIAGNOSED TYPE 2 DIABETES**

Early, tight glycaemic control in patients with type 2 diabetes has been shown to result in better outcomes in terms of microvascular disease and longer term observation revealed better macrovascular and mortality outcomes even if control is relaxed later in the course of the disease. [22] The goal should be to achieve an HbA1c of <6.5% within 6 months of diagnosis based upon these analyses. [6]

In this UKPDS study, in addition to age at diagnosis, an important predictor of death in patients with recent onset of type 2 diabetes was the HbA1c achieved 3 months after diagnosis. Compared with patients with a 3 month HbA1c of <6.5%, mortality rate was almost doubled in patients with an HbA1c of ≥8.5, even after correcting for age at diagnosis [7]

Various guidelines generally recommend a target HbA1c of less than 6% to 7% [2] for newly diagnosed and uncomplicated patients. Despite increasingly stringent guidelines for glycaemic control, over 60% of patients do not reach recommended glycaemic goals. In one Australian study, less than half (47.7%) of patients (n=3893) with type 2 diabetes seen in general practice had an HbA1c of <7.0% and 25% had an HbA1c of >8%. [8]

Increased rates of hypoglycaemia and weight gain may accompany any such "tight" lowered HbA1c goals for newly diagnosed patients.

The RACGP NFSI Diabetes Network wishes to emphasize the not inconsiderable impact of hypoglycaemia. As illustrated in the attached trials, such impacts lead to increased rates of hospitalisation, complications and reduction in overall adherence. Thus, this increased burden on patients' and clinical service utilisation could be avoided by alternatives, which reduce such risks, such as gliptin therapy. Certain patient groups such as the elderly are most at risk of this 'burden' of disease as shown in the higher numbers of people with diabetes in the age of 65 years or older requiring hospitalization from hypoglycaemia. [9] Further as per the Noh et al [10] study of hospital patients reported that over 9-12 months, severe hypoglycaemia occurred in 7% of those on sulphonylureas or on insulin for less than 2 years, and in 25% of those on insulin for more than 5 years
This translates to increased average annual healthcare cost per person with diabetes. Doubling of costs from a baseline of $4,025 to $9,645 occurs in people with diabetes developing complications [5]

In recent meta-analyses [13,18], the newly TGA listed agents such as oral DPPIV agents and injectable GLP1 agonists, as combination therapy, help address the dual issues of hypoglycaemia and weight gain while achieving equivalent glycaemic goals as agents such as sulphonylureas and insulin. Balancing this is the low incidence of serious adverse events identified with the oral gliptin agents. Known side effects, and clinical training and patient education/support requirements, for the GLP1 agonists have seen a smaller increase in use of these agents outside of PBS restrictions. This may be assumed rightly to be within the realm of specialist practitioners because of the factors mentioned above.

To summarise, by quoting a National Prescriber Service general practice focused document: "The balance of risks and benefits of intensive blood glucose control should be considered on an individual patient basis. Lower HbA1c targets may benefit younger patients or those newly diagnosed. However, in older patients or in those with long-standing disease the risk of hypoglycaemia and adverse events may outweigh any benefit" [14]

IMPLICATIONS

- Thus, these newer agents, on this evidence base have gained clinical traction for use as either equivalent to second line diabetes agents such as second generation sulphonylureas with less clinical relative and absolute contraindications. As well, in combination therapy as third line agents, efficacy in HbA1c lowering has been established as a step before insulin initiation without the increased patient burden of such therapy such as injection technique education and self monitoring of blood glucose.

- Clinical Education gaps exist in ensuring patients with newly diagnosed diabetes are achieving goals that may result in longer term clinical complication reduction with less burden of disease. (The "legacy" effect)

- Balancing this view is that prospective analyses of long term cardiovascular benefit from any such interventions for newly diagnosed patients with type 2 diabetes is yet to be established conclusively. This is further addressed in the following section.

B) TYPE 2 DIABETES WITH ESTABLISHED CARDIOVASCULAR DISEASE OR HIGH CARDIOVASCULAR RISK

Arising from the ACCORD study [17] where intensive treated cohorts with a median HbA1c levels after 1 year were 6.4% (46 mmol/mol) in the intensive therapy group compared to 7.5% (58 mmol/mol) in the standard therapy group, there emerged an increased risk of all cause mortality and cardiovascular death, especially in those with existing cardiovascular disease and a baseline HbA1 C > 8%. Thus those with most risks clustered in those whose intensive treatment had the greatest gradient to goal.

The CONTROL meta-analysis [18] pooled the data of 27 049 participants from this ADVANCE trial and three other significant randomized controlled trials (UKPDS, ADVANCE and VADT).

Other meta-analyses [19] support the conclusion is summarized in that in the patients undergoing intensively lowering of blood glucose there is a moderate cardiovascular risk benefit but no lowering of overall mortality or stroke, and more than double the incidence of severe hypoglycaemia.

IMPLICATIONS

The RACGP NFSI Diabetes Network supports ongoing assessment of the glycaemic agents with respect to cardiovascular risk assessment in subpopulations such as those with established cardiovascular disease or elevated cardiovascular risk.

The quality use of medicines implications could be that, education on the appropriate use of agents that achieve glycaemic goal without raising cardiovascular risks, as well as minimising risks of hypoglycaemia, may have a greater safety profile. Additionally if agents demonstrate low levels of significant side effects this would further provide improved patient utility versus burden, as a not insignificant clinical benefit.

Currently, in theory, newer oral gliptins match these clinical requirements in this patient group. However, as prospective cardiovascular trials are yet to be published, as knowledge currently stands, it is still not fully established whether these newer agents provide cardiovascular safety reassurance. This evidence will emerge over the next 2 years or so.

SECOND LINE THERAPY FOR TYPE 2 DIABETES

Current guidelines emphasize the need for early Lifestyle modification before introduction of any medication. [1-4]

All guidelines emphasize the need for initial introduction of metformin as monotherapy. [1-4]

Failure of such monotherapy and need for additional second line agent has been studied to average 12% of patients per annum on Metformin monotherapy. [20] Within the UKPDS study it emerged that to ensure patients were kept below a HBA1c of 7% (53 mmol/mol additional medication was required by the 3rd year of assessment, in 50% of patients. [21]

Current Australian general practice prescribing algorithms emphasize the need to consider sulphonylurea agents as the first PBAC subsidised 2nd line agents beyond metformin monotherapy. [1-4]

Current restrictions or streamlined authorization of PBS subsided scripts has 'wording' that was open to clinical interpretation or mis-interpretations, as exampled in the recent DUSC diabetes medication review which emphasized an assumption that words such as intolerance and contraindication traced back to product information wording.

"the committee noted that true contraindication to sulphonylurea is low (according to the Product Information primarily severe hepatic dysfunction and severe renal impairment).The committee noted that to establish intolerance to a sulphonylurea, a trial of the medicine is required. The utilization analysis showed that the proportion of patients co-administered metformin with a sulphonylurea for a short period of time that would be consistent with a trial of treatment, was very low"

IMPLICATIONS

The RACGP NFSI Diabetes Network collectively agree that clinicians would wish to emphasise that in clinical practice "relative" contraindications (oft listed under precautions in product information) are considered in choosing pharmaceutical agents along side the listed "absolute" contraindications as listed in the above DUSC/PBAC review documentation. The RACGP NFSI Diabetes network agrees with the definition of "Intolerance" as outlined.

The document (attachment A) demonstrates that there is a divergence between the narrow DUSC/PBAC review assessment of "Intolerance" and "Contraindication" and how and when clinicians apply interpretation of "Precautions" (see attachment C). These terms in clinical practice would not be seen to be mutually exclusive. This may then give rise to clinically appropriate initiation of alternate second line agents whereby relative and absolute contraindications are individually considered before prescription recommendation.

The RACGP NFSI Diabetes Network request that arising from this and future DUSC reviews, any such PBAC wording of Authority Listing for diabetes medications, THAT, there be a process developed whereby consultation of appropriate clinical guideline development group and RACGP NFSI Networks BE IMPLEMENTED, such that any such Authority or restriction wording encapsulates the quality use of medicines APPLICABLE TO GENERAL PRACTICE as well as fulfilling PBAC intentions and outcomes.

REFERENCES

1. Colagiuri S, Dickinson S, Girgis S, Colagiuri R. National Evidence Based Guideline for BloodGlucose Control in Type 2 Diabetes. Diabetes Australia and the NHMRC, Canberra 2009. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di19-diabetes-blood-glucose-control.pdf
2. Cheung NW, Conn JJ, d'Emden MC, et al. Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus. MJA 2009; 191: 339–44.
3. http://www.diabetesaustralia.com.au/Documents/DA/Publications/13.04.08%20DMiGP%20Web%20Version.pdf
4. http://www.racgp.org.au/your-practice/guidelines/diabetes/
5. Diabetes: the silent pandemic and its impact on Australia http://www.diabetesaustralia.com.au/Documents/DA/What's%20New/12.03.14%20Diabetes%20management%20booklet%20FINAL.pdf
6. Deed G, Barlow j, Kuo I. Early and tight glycaemic control - The key to managing type 2 diabetes. Australian Family Physician Vol. 41, No. 9, September 2012
7. Kerr D, Partridge H, Knott J, Thomas PW. HbA(1c) 3 months after diagnosis predicts premature mortality in patients with new onset type 2 diabetes. Diabet Med 2011;28:1520–4.
8. 5. Macisaac RJ, Jerums G, Weekes AJ, Thomas MC. Patterns of glycaemic control in Australian primary care (NEFRON 8). Intern Med J 2009;39:512–8.
9. McCoy RG et al. Increased mortality of patients with diabetes reporting severe hypoglycemia.Diabetes Care 2012;35:1897–901; 2.
10. Signorovitch, J et al. Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs. Diabetes Obes Metab. 2013 April; 15(4): 335–341.Published online 2012 November 22.
11. Table7 :http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442453548
12. Noh, R. M., Graveling, A. J. & Frier, B. M. 2011. Medically minimising the impact of hypoglycaemia in type 2 diabetes: a review. Expert Opin Pharmacother, 12, 2161-75.
13. Canadian Agency for Drugs and Technologies in Health. Clinical Review: Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and a Sulfonylurea. Ontario: CADTH, 2010
14. TYPE 2 DIABETES: PRIORITIES AND TARGETS BACKGROUND MATERIALS JUNE 2012 www.nps.org.au
15. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011; 343: d4169. doi: 10.1136/bmj.d4169.
16. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010; 33: 1389–94.
17. The Action to Control Cardiovascular Risk in Diabetes Study Group Effects of Intensive Glucose Lowering in Type 2 Diabetes The Action to Control Cardiovascular Risk in Diabetes Study Group N Engl J Med 2008; 358:2545-2559 June 12, 2008
18. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288-98.
19. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009; 373: 1765–72.
20. Brown, J et al Secondary Failure of Metformin Monotherapy in Clinical Practice. Diabetes Care March 2010 vol. 33 no. 3 501-506

21. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837–53.
22. Holman RR, Paul SK, Bethel MA et al. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577–89.

ATTACHMENT A

Product Information – Australia

Terry White Chemists Gliclazide Tablets Page 1

TERRY WHITE CHEMISTS GLICLAZIDE TABLETS

NAME OF THE MEDICINE

Gliclazide

Chemical Name: 1-(3-azabicyclo[3.3.0]oct-3-yl)-3-*p*-tolylsulphonylurea.

Structural Formula:

Molecular Formula: $C_{15}H_{21}N_3O_3S$

Molecular Weight: 323.4

CAS Registry Number: 21187-98-4

DESCRIPTION

Gliclazide is a white or almost white powder which is practically insoluble in water.

Gliclazide tablets are intended for oral administration. Each tablet contains gliclazide 80 mg.

They are round, white, flat-sided tablets with bevelled edges, engraved “APO” over “80” on one side, cross-scored on the other side.

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, lactose, microcrystalline cellulose.

PHARMACOLOGY

Pharmacodynamics

Gliclazide is a sulfonylurea hypoglycaemic agent which restores the diminished first-phase of insulin secretion noted in non-insulin dependant diabetes mellitus. Gliclazide stimulates insulin secretion from functional pancreatic □-cells and increases the sensitivity of the □-cells to a glucose stimulus (some residual □-cell function is therefore necessary).

Any long-term hypoglycaemic activity of gliclazide is primarily due to its ability to maintain an effect on insulin secretion, although extrapancreatic effects may also be involved. Extrapancreatic effects demonstrated for gliclazide include improvement in insulin mediated glucose utilisation and potentiation of postreceptor insulin sensitive pathways. At normal therapeutic doses in man, gliclazide reduces platelet

adhesiveness and aggregation.

Pharmacokinetics

Absorption

Following the absorption of gliclazide peak serum concentrations are reached within 4 to 6 hours. Single dose studies have demonstrated that maximal falls in blood glucose levels (23% for an 80 mg dose; 30% for a 160 mg dose) occur approximately five hours after drug administration. Following a dose of 160mg,

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a 20% reduction in blood glucose levels was still evident after nine hours. The half-life of gliclazide is approximately 12 hours.

Distribution

Gliclazide is distributed to the extracellular fluid. In animals, high concentrations of the drug were found in the liver, kidneys, skin, lungs, skeletal muscle, intestinal and cardiac tissue. Penetration of gliclazide into the central nervous system was negligible. Gliclazide crosses the placental barrier and penetrates the foetus. The apparent volume of distribution of gliclazide (20 to 40% expressed as a percentage bodyweight) is low and probably reflects the high degree of protein binding (94.2% at a plasma concentration of approximately 8 µg/mL).

Metabolism and Excretion

Little information is available on the metabolism of gliclazide. At least eight metabolites (three major) have been identified by thin layer and gas-liquid chromatography. Some of these are glucuronic acid conjugates; only one of the metabolites has been identified rho-toluene sulfonamide). The liver is the probable site of metabolism.

Approximately 70% of the administered dose appears to be excreted in the urine and 11% in the faeces. The urinary excretion of the drug is slow and the maximum rates do not occur until 7 to 10 hours after initial administration. The metabolic products are detectable in the urine 120 hours after oral administration. Faecal elimination is usually complete within 144 hours of oral administration.

INDICATIONS

Diabetes mellitus of the maturity onset type, which cannot be controlled by diet alone.

CONTRAINDICATIONS

 Diabetes complicated by acidosis, ketosis, pre-coma or coma, or in patients with a history of repeated episodes of ketoacidosis or coma.

 Juvenile onset (Type I) diabetes, unstable or brittle diabetes – sulfonylurea hypoglycaemic agents are not effective in these conditions.

 Severe renal or hepatic insufficiency.

 Known hypersensitivity to gliclazide, other sulfonylureas, sulfonamides, or any of the inactive ingredients listed under **PRESENTATION AND STORAGE CONDITIONS**.

 Treatment with miconazole (refer to **Interactions with Other Medicines**)

 Pregnancy and lactation (refer to **PRECAUTIONS - Use in Pregnancy and Use in Lactation)**.

It is generally not recommended to use this agent in combination with phenylbutazone or danazol (refer to **Interactions with Other Medicines**).

PRECAUTIONS

Acute Complications such as Severe Trauma, Fever, Infection or Surgery

These acute complications provoke additional metabolic stress, which accentuate the predisposition to hyperglycaemia and ketosis. Patients presenting with such conditions may require insulin to maintain control. It is not appropriate to increase the dosage of gliclazide.

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Hypoglycaemia

The prescriber needs to educate the patient to be alert to the signs and symptoms of hypoglycaemia (refer to **ADVERSE EFFECTS** and **OVERDOSAGE)**, and discuss prevention/treatment strategies with the patient at consultation.

Hypoglycaemia may occur following administration of sulfonylureas. Rarely hypoglycaemia may be severe and prolonged, and may require hospitalisation where glucose infusion may need to be continued for several days.

Careful selection of patients and of the dose used are necessary to avoid hypoglycaemic episodes. Experience with sulfonylureas shows that hypoglycaemia can recur even when measures such as the intake of carbohydrate such as sugar are initially effective. If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or

even hospitalisation is required.

Patients must be warned that artificial sweeteners are not recommended in the treatment of hypoglycaemia as they have negligible effect.

Patients who may be particularly sensitive to antidiabetic agents include those who are elderly, undernourished or who have poor general health, and patients with adrenal insufficiency or hypopituitarism. Hypoglycaemia may be difficult to recognise in elderly patients and those receiving beta-blockers.

Close observation and careful initiation and adjustment of dosage is mandatory in patients who are elderly and debilitated, malnourished, semistarved or simply neglecting dietary restrictions. In such patients severe hypoglycaemia may occur with all sulfonylureas and may require corrective therapy over a period of several days. Certain conditions such as alcoholism, insulinoma, adrenal thyroid and pituitary insufficiency increase the sensitivity to sulfonylureas and may dispose to hypoglycaemia.

This treatment should only be prescribed if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is delayed, an inadequate amount of food is consumed or the food is low in carbohydrate.

Hypoglycaemia is more likely to occur during periods of low-calorie diet, following prolonged or strenuous exercise, following alcohol intake or during treatment with a combination of hypoglycaemic agents.

Poor blood glucose control

Blood glucose control in treated patients may be jeopardised by: fever, trauma, infection or surgical intervention. It may be necessary to discontinue treatment and to administer insulin in these cases.

The efficacy of oral antidiabetic agents often decreases in the long term. This may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure and should be distinguished from primary failure, when the drug is ineffective as first-line treatment. However, before classifying the patient as a secondary failure, dose adjustment and reinforcement of dietary measures should be considered.

Glucose-6-phosphate dehydrogenase deficiency (G6PD)

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia.

Since gliclazide belongs to the chemical class of sulfonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Lactose intolerance

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

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Laboratory tests

Glycated haemoglobin should be monitored regularly. Blood glucose measurement may also be useful.

Monitoring of Diabetic State

As with other antidiabetic therapies, patients must be under close medical supervision. Particular care must be taken during the initial period of stabilisation. Patients treated with gliclazide should be monitored regularly to ensure optimal control of the diabetic state, and where necessary, for adjustment of dosage.

It is not generally recommended that insulin treated patients be transferred to gliclazide. Patients who have been previously treated with sulfonylureas or biguanides alone or in combination may be transferred to gliclazide.

When gliclazide is administered as sole therapy to patients who have previously required combination therapy (e.g. biguanides and sulfonylureas), careful observation is essential during the transitional phase.

Renal and hepatic insufficiency

Severe renal or hepatic insufficiency may affect the distribution of gliclazide and hepatic insufficiency may also reduce the capacity for neoglucogenesis. These two effects increase the risk of severe hypoglycaemic reactions. A hypoglycaemic episode in these patients may be prolonged and appropriate management should be initiated.

Patient awareness

Comprehensive instructions must be given to the patient about the nature of the disease and what must be done to detect and prevent complications.

Use in Pregnancy (Category C_1)

Gliclazide should not be used in pregnant women. It is important to achieve strict normoglycaemia during pregnancy. Oral hypoglycaemic agents should be replaced by insulin.

The sulfonylureas may enter the foetal circulation and cause neonatal hypoglycaemia. In animal studies embryotoxicity and/or birth defects have been demonstrated.

Gliclazide should not be used in pregnant women although animal studies of gliclazide have not shown any teratogenic effect. From a clinical point of view, there are no adequate data to allow evaluation of the possible malformative or foetotoxic effects of gliclazide, when administered during pregnancy.

Use in Lactation

In the absence of data on the transfer of gliclazide into breast milk, and given the risk of neonatal hypoglycaemia, breast-feeding is contra-indicated during treatment with this product.

Carcinogenicity

No animal studies have been performed that investigate the carcinogenic potential of gliclazide.

Effects on ability to drive and use machines

Patients should be made aware of the signs and symptoms of hypoglycaemia and should be careful if driving or operating machinery, especially at the beginning of treatment.

1 *Australian Categorisation Definition of Category C*: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

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INTERACTIONS WITH OTHER MEDICINES

Disturbances of Blood Sugar Control

Thiazide diuretics may aggravate the diabetic state and caution should be used when administering thiazide diuretics to patients on gliclazide therapy. Other drugs which may adversely affect blood sugar control with hypoglycaemic agents include barbiturates, chlorpromazine, danazol, glucocorticoids, oestrogens and progestogens, salbutamol, terbutaline.

Potentiation of Hypoglycaemic Effect

Certain drugs may potentiate the effect of gliclazide and thereby increase the risk of hypoglycaemia. These include insulin, acarbose, biguanides, sulfonamides, oxyphenbutazone, phenylbutazone,

clofibrate, salicylates (high doses), coumarin derivates, chloramphenicol, MAOIs, □-blockers, cimetidine, ACE inhibitors, ethanol, fluconazole and miconazole (Note: miconazole is contra-indicated with gliclazide), H_2 receptor antagonists and nonsteroidal anti-inflammatory agents.

Warn the patient and emphasise the importance of self-monitoring of blood glucose levels.

It may be necessary to adjust the dose of the antidiabetic agent during treatment with these substances.

Anticoagulant Therapy

Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment.

Adjustment of the anticoagulant may be necessary

Alcohol

Acute alcohol intoxication potentiates the hypoglycaemic action of all sulfonylurea agents. Furthermore, ingestion of alcohol may cause a disulfiram-like reaction with characteristic flushing of the face, throbbing headache, giddiness, tachypnoea, tachycardia or angina pectoris.

Chronic alcohol abuse may, as a result of liver enzyme induction stimulate the metabolism of sulfonylurea drugs and shorten plasma half life and duration of action.

ADVERSE EFFECTS

Adverse reactions have occurred in some 12% of cases in clinical studies. However, approximately 2% of patients were withdrawn from therapy because of adverse reactions, notably hypoglycaemia, gastrointestinal disturbances (constipation, nausea, epigastric discomfort and heartburn), dermatological reactions (rash and transient itching), and biochemical abnormalities (elevated serum creatinine, increased serum alkaline phosphatase, raised serum AST, elevated BUN and raised serum bilirubin). Headache, slight disulfiram like reactions and lassitude have also been reported.

Serious reactions which have been reported with other sulfonylureas are leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, cholestatic jaundice and gastrointestinal haemorrhage. These reactions have not been reported with gliclazide. (see also **Class attribution effects**, near the end of this section).

Hypoglycaemia (refer to PRECAUTIONS and OVERDOSAGE)

As is the case with all sulfonylurea drugs, hypoglycaemic reactions have been reported following gliclazide administration. However, a number of studies have shown that hypoglycaemia is less

common with gliclazide than with glibenclamide.

In long-term comparative studies, the percentage of patients experiencing hypoglycaemic episodes was similar between patients treated with gliclazide MR (11.6%) and those treated with gliclazide 80 mg (11.1%).

Possible signs and symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and/or death.

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In addition, signs and symptoms of hypoglycaemic adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

Adverse events that were reported in at least 2.0% of patients, in long-term controlled clinical studies, are presented in the following table. The most frequent adverse events were not specifically related to the disease (such as respiratory infections or back pain).

Treatment emergent adverse events* (listed by body system) occurring in ≥ 2.0% of patients in long-term controlled clinical trials

Gliclazide 80 mg

(n=734) %

Gliclazide MR

(n=728) %

Resistance mechanism

Viral infection

5.6

7.7

Respiratory

Rhinitis

Bronchitis

Pharyngitis

Upper respiratory infection

Coughing

4.6

4.6

3.5

3.7

2.0

4.4

4.4

4.3

3.3

2.1

Musculo-skeletal

Back pain

Arthralgia

Arthrosis

4.1

3.5

2.2

5.2

3.0

2.2

Secondary term

Inflicted injury

4.5

4.3

Body as a whole

Headache

Asthenia

4.6

2.6

3.8

2.2

Cardiovascular

Hypertension

Angina pectoris

3.7

2.2

3.2

2.1

Urinary

Urinary tract infections

3.0

2.6

Gastrointestinal

Diarrhoea

2.0

2.5

Central, peripheral, nervous

system

Dizziness

2.3

2.2

Metabolism & nutrition

Hyperglycaemia

2.2

1.9

* whatever the relationship to treatment

Gastrointestinal disturbances (reported with gliclazide), including nausea, dyspepsia, diarrhoea and constipation may be avoided or minimised if gliclazide is taken with breakfast.

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The following adverse events have been rarely reported in patients taking gliclazide:

- Skin and mucosae reactions: pruritus, urticaria, maculopapular rashes, rash, erythema and bullous reactions

- Haematological disorders (as with other sulfonylurea drugs): a few rare cases of anaemia, leucopenia, thrombocytopenia and agranulocytosis

- Occasional elevations of serum creatinine, blood urea nitrogen, serum bilirubin and hepatic enzymes (AST, ALT, alkaline phosphatase) levels, and exceptionally, hepatitis. **Treatment should be discontinued if cholestatic jaundice appears.**

These symptoms usually disappear after discontinuation of treatment.

Because of the glucose-lowering effect of gliclazide, transient visual disturbances may occur on initiation of treatment due to changes in blood glucose levels.

Class attribution effects

Cases of erythrocytopenia haemolytic anaemia, pancytopenia, hyponatraemia and allergic vasculitis, have been described for sulphonylureas.

With sulphonylureas cases were also observed of elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulphonylurea or led to life-threatening liver failure in isolated cases.

DOSAGE AND ADMINISTRATION

The dosage of gliclazide should be carefully titrated to maintain optimal control at the various possible dose levels. Dosage should be initiated at 40 mg (1/2 tablet) daily and may be increased if necessary up

to 320 mg (4 tablets) daily. Doses up to 160 mg daily may be taken in a single dose but preferably at the same time each morning. Doses in excess of 160 mg should be taken in divided doses in the morning and evening.

In general, the dosage will depend on the severity of the glycaemia. Ongoing adjustments should be made in order to obtain the optimal response at the lowest dosage. Treatment with gliclazide does not obviate the necessity of maintaining standard dietary regulations

Transferring to gliclazide: Patients who have been previously treated with sulfonylureas or biguanides alone or in combination may be transferred to gliclazide. When gliclazide is administered as sole therapy to patients who have previously required combination therapy (e.g. biguanides and sulfonylureas), careful observation is essential during the transitional phase.

OVERDOSAGE

Symptoms

Manifestations of severe hypoglycaemia result from overdosage. Hypoglycaemia caused by sulfonylurea agents differs in several aspects from insulin coma. Warning symptoms are often absent, neurological syndromes are frequent and coma is often prolonged.

Treatment

Moderate symptoms of hypoglycaemia (without loss of consciousness or neurological signs), should be corrected by carbohydrate intake, dose adjustment and/or modification of diet. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

Severe hypoglycaemic reactions are possible (with coma, convulsions or other neurological disorders) and should be treated as a medical emergency, requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50mL of concentrated glucose solution (20 to 30%). This should be followed by continuous infusion of a

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more dilute glucose solution (10%) at a rate necessary to maintain blood glucose levels above 5mmol/L.

It is recommended that patients should be monitored closely for a 48 hour period at least.

Plasma clearance of gliclazide may be prolonged in patients with hepatic disease. However, due to the strong binding of gliclazide to proteins, dialysis is not effective in these patients.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Terry White Chemists Gliclazide 80 mg tablets

Round, white, flat-sided tablets with bevelled edges, engraved “APO” over “80” on one side, cross-scored on the other side.

Blister pack in cartons containing 100 tablets.

AUST R Number 80087

* Not all strengths, pack types and/or pack sizes may be available.

Storage

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd

16 Giffnock Avenue

Macquarie Park NSW 2113

Terry White Chemists is a registered trade mark of Symbion Pty Ltd.

POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

Date of TGA Approval : 7 August 2002

Date of most recent amendment: 27 September 2012

ATTACHMENT B

TGA approved indications for diabetes agents versus PBAC approval is

FOR DPPIV AGENTS

3540

Dual oral combination therapy with metformin or a sulfonylurea

Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The date and level of the qualifying HbA1c must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:

(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or

(b) red cell transfusion within the previous 3 months.

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records

GLP 1 – currently Exenatide

3540 – as above

3542

Triple oral combination therapy with metformin and a sulfonylurea

Type 2 diabetes, in combination with metformin and a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.

The date and level of the qualifying HbA1c must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:

(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or

(b) red cell transfusion within the previous 3 months.

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records

ATTACHMENT C

PRECAUTIONS include,

Patients who may be particularly sensitive to antidiabetic agents include those who are elderly, undernourished or who have poor general health, and patients with adrenal insufficiency or hypopituitarism. **Hypoglycaemia may be difficult to recognise in elderly patients and those receiving beta-blockers.***

Close observation and careful initiation and adjustment of dosage is mandatory in patients who are elderly and debilitated, malnourished, semistarved or simply neglecting dietary restrictions. In **such patients severe hypoglycaemia may occur with all sulfonylureas*** and may require corrective therapy over a period of several days. Certain conditions such as alcoholism, insulinoma, adrenal thyroid and pituitary insufficiency increase the sensitivity to sulfonylureas and may dispose to hypoglycaemia.

This treatment should only be prescribed if the patient is likely to have a regular food intake (including breakfast)*. It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is delayed, an inadequate amount of food is consumed or the food is low in carbohydrate.

Hypoglycaemia is more likely to occur during periods of low-calorie diet, following prolonged or strenuous exercise, following alcohol intake or during treatment with a combination of hypoglycaemic agents.

(* - NFSI Diabetes network emphasis)