EML Section 18.5 – Insulin and other medicines used for diabetes

Comparative Safety and Efficacy of Glibenclamide in the Elderly

Should elderly patients with type 2 diabetes be treated with glibenclamide (glyburide) or different sulfonylurea?

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Acronyms and Abbreviations:

BNF – British National Formulary

CI – Confidence interval

CV – Cardiovascular

DM – Diabetes Mellitus

EC – Expert Committee

EML – Essential Medicines List

FDA – Food and Drug Administration

HbA1c – Glycosylated hemoglobin

LMICs - Low- and Middle-Income Countries

MSH – Management Sciences for Health

NEML – National Essential Medicines List

RCT – Randomized controlled trial

SFU – Sulfonylureas

SRA – Stringent Regulatory Authority

TGA – Therapeutics Goods Administration

UK – United Kingdom

US – United States of America

USD – United States dollar

WHO – World Health Organization

Executive Summary

This application reviewed the comparative safety and efficacy of 4 second generation sulfonylureas (2nd generation SFUs) for the treatment of type 2 non-insulin dependent diabetes in elderly patients for the Essential Medicines List for adults as requested by the 18th WHO Expert Committee on the Selection and Use of Essential Medicines. The medications reviewed included the 2nd generation SFU currently on the EML – glibenclamide, also called glyburide. This medication was compared with three other 2nd generation SFUs commonly used and widely available worldwide – gliclazide, glimepiride and glipizide. The application also analyzed the cost of the four medications as well as their availability of NEMLs of 40 low and middle-income countries.

Compared with other sulfonylureas, glyburide has been associated with an increased risk of severe hypoglycemia, especially in the elderly. Evidence show the increased relative risk of hypoglycemia and the resulting harm with use of glibenclamide versus any of the other second generation SFUs, particularly gliclazide and glipizide. The data unequivocally recommends against the use of glibenclamide in elderly patients.

A retrospective, cohort study of more than 13,000 patients concluded that glyburide had the highest rate of hypoglycemia at 16.9 per 1000 person-years, compared to all other SFUs. The authors also concluded that the physiological changes associated with increasing age such as declining renal and hepatic function, as well as polypharmacy and concurrent illnesses additionally predispose the elderly to hypoglycemia; this predisposition is further compounded by use of glibenclamide. Another retrospective, cohort study of more than 33,000 patients in the UK showed that the risk of hypoglycemia was higher with glibenclamide when compared to other SFUs. The authors also concluded that patients older than 65 years, were at higher risk of hypoglycemia versus adults less than 65 years of age with a relative risk of 1.27 (CI 1.06-1.51). A 2007 meta-analysis of 21 studies showed that there is an increased risk of hypoglycemia with glibenclamide by 52% than with other insulin secreting anti-diabetes therapies and 83% higher risk compared to other SFUs.

The same meta-analysis also showed that based on HbA1c results, compared to other SFUs, including gliclazide, glimepiride and glipizide, glibenclamide did not have an increased efficacy in treatment of diabetes.

Based on a review of safety, efficacy, cost and NEML availability of glibenclamide, gliclazide, glipizide and glimepiride, the recommendations are as follow:

1. Glibenclamide 2.5mg and 5mg tablets should remain on the EML with age restriction recommending against use in patients older than 6o years of age.
2. Gliclazide 80mg tablet should be added to the EML for use in the elderly with type 2 diabetes, with a square box designation so as to indicate that other second general sulfonylureas (other than glibenclamide) are an acceptable alternative.

Review

I. Background and Rationale for the review

Diabetes mellitus is a chronic disease that occurs when the pancreas does not produce enough insulin leading to hyperglycemia and requires life-long pharmacological and non-pharmacological management to prevent complications such as cardiovascular disease, retinopathy, nephropathy, and neuropathy.[1-4] Type 2 diabetes mellitus is the most common form of diabetes comprising of 90% to 95% of all diabetes cases.[2] An estimated 346 million people worldwide live with diabetes, resulting in 3.4 million deaths in 2004, with more than 80% of these deaths occurring in low- and middle income countries.[5] The fastest growing age group of people with diabetes is between 40 to 59 years.[6] The worldwide 2011 estimated prevalence of diabetes is the elderly population (60 years and above) is between 15% to 20%.[6] It is projected that the death burden from diabetes will double by the year 2030 to around 7 million.[5] According to the 2010 WHO report on NCDs, the estimated prevalence of diabetes in 2008 was about 8% for men and women in low-income countries and 10% for both sexes in upper-middle-income countries with the highest global prevalence of diabetes in Eastern Mediterranean Region and Region of the Americas.[7] The high prevalence rate is of concern since diabetes in the leading cause of renal failure, visual impairment and blindness and increases the risk of lower limb amputation by at least 10 times.[7] Additionally, patients living with diabetes may need 2 to 3 fold more health-care resources compared to people without diabetes and diabetes care may require allocation of up to 15% of national health care budgets.[7] Furthermore, given the close link between poverty and NCDs, the NCDs impose a disproportionate burden on low and middle income countries (LMICs).[7]

The 18th WHO Expert Committee on the Selection and Use of Essential Medicines (18th EC) in 2011 requested a review concerning the safety of sulfonylureas, a class of oral anti-diabetic agents, in the elderly patient population, to determine if updates to the EML are needed. [8] A review of safe use of medications in the elderly population is of great importance. A 12-month retrospective cohort study of elderly patients on Medicare (Federally funded healthcare plan) in the US identified medication related adverse event rate of 50.1 per 1000 person years with a preventable rate of 13.7 per 1000 person years.[9] The study identified 27.6% of the ADEs were preventable, while 58% of these errors occurred due to improper prescribing and 10.9% were related to anti-diabetic medications.[9]

Currently, the EML contains one second generation sulfonylurea, glibenclamide, also known as glyburide, for treatment of adults, including the elderly, living with diabetes. This document will conduct comparative analysis of four second generation SFUs – glimepiride, glipizide, gliclazide and glibenclamide – to determine their safety and efficacy in the elderly.

The review will also 1) conduct a cost-comparison of these agents, 2) provide an overview of the current availability of the three medications in questions in LMICs by surveying NEMLs of 40 nations, and 3) provide information on regulatory status of these agents in the US, UK and Australia. The regulatory status in US, UK and Australia was selected as an initial reference

point given the stringent review and approval process required for therapeutic approval by these agencies and due to the availability of the databases in English. Glimepiride, glipizide and glibenclamide were selected for review due to their approval for use in DM by three SRAs. However, gliclazide is also reviewed due to the extensive use and availability of this agent worldwide; gliclazide is approved for use in diabetes by UK and Australia SRAs, but it is not approved by the FDA in the US. All four medications are off-patent.

II. Search Methods

1. Methods for compiling evidence on safety and efficacy

The purpose of this review was to present comparative safety and efficacy information on four sulfonylureas (anti-diabetes medications); therefore, the search was focused to answer this question.

The four agents under review: glimepiride, glipizide, gliclazide and glibenclamide (glyburide).

The Cochrane library and PubMed databases were searched for systematic reviews or meta-analysis, clinical studies, observational studies and literature reviews evaluating or presenting information on safety and efficacy (either comparative or placebo-controlled) of glimepiride, glipizide, gliclazide and glibenclamide (glyburide) up to October 2012. The following strategy was employed:

1. Glibenclamide compared to glimepiride, glipizide, and/or gliclazide for safety and/or efficacy.
2. Glimepiride compared to glipizide, gliclazide and/or glibenclamide (glyburide) for safety and/or efficacy.
3. Glipizide compared to glimepiride, gliclazide and/or glibenclamide (glyburide) for safety and/or efficacy.
4. Gliclazide compared to glimepiride, glipizide, and/or glibenclamide (glyburide) for safety and/or efficacy.
5. Glimepiride, glipizide, gliclazide and/or glibenclamide (glyburide) compared to placebo for safety and/or efficacy.
6. The term ‘hypoglycemia’ was also used as a measure of comparative safety.
7. Only standard, regular, original or immediate release tablet/capsule formulations were reviewed for pharmacokinetic, safety or efficacy; modified or extended release or other formulations were excluded from the review.
8. The search was limited to publications in English.
9. A title review was conducted to identify relevant results followed by an abstract review.

The online databases of three stringent regulatory authorities were also searched for pertinent information: FDA (United States), TGA (Australia), and MHRA (UK). [10-12] Other online

databases searched were: British National Formulary, and Micromedex and Lexi-Comp (clinical pharmacy databases). [13-15] All SRAs and databases were selected based on their online availability in English.

The following search terms were used:

- glimepiride, glipizide, gliclazide, glibenclamide, glyburide, diabeta, diamicron, glucotrol, amaryl, sulfonylurea, sulphonylurea, hypoglycemia, hypoglycaemia, efficacy, safety, pharmacokinetics, pharmacodynamics, elderly, adults, older adults.
- [AND / OR] terms were used to search for comparative trials, studies and reviews.

2. Methods for survey of medication availability on NEMLs

The WHO Essential Medicines website was used to reference NEMLs of 40 LMICs to determine how many of the surveyed nations had four medications in question on their NEML.[16]

The NEML review was limited to nations that published their respective NEMLs in English, French or Spanish.

3. Methods for cost comparison

MSH 2011 International Drug Price Indicator Guide was referenced first to obtain median buyer price per unit.[17] When the cost of a medication was not available from the MSH guide, US market based prices for prescription medications were used for comparison using an online database, Lexi-Comp.[14]

4. Definition of an elderly person

For the purposes of this review, the definition of elderly was selected based on initial literature review. In the reviewed literature, the age at which an individual may be considered ‘old’ or ‘elderly’ was variable. Some of the literature included in this review considers individuals older than 60 years of age as elderly, while other publications used 65 years as the cutoff age. Hence, to provide a comprehensive analysis, this review considers 60 years of age and older as the definition of an elderly person.

III. Pharmacokinetic and Pharmacodynamic profile of sulfonylureas used in diabetes

Sulfonylureas aim to reduce diabetes associated hyperglycemia by acting on the pancreatic beta-cell channels (ATP-K channel) to facilitate insulin secretion. [18] Table 1 below categorizes the various PK parameters of the three SFUs under consideration in this review. The primary difference between glibenclamide and the other SFUs is the prolonged half-life of glibenclamide at 10 hours compared average half-life of 5 hours for glimepiride and 2 to 5 hours for glipizide.[19-21] The PK parameters of half-life, elimination and volume of distribution are also increased to a greater extent for glibenclamide compared to glimepiride and glipizide. [19-24] However, all sulfonylureas are hepatically metabolized and renally cleared, therefore, are subject to slower elimination in the elderly due to the age-associated decrease in renal function. [19-24] Furthermore, compared to glipizide or glimepiride, glibenclamide has a higher affinity for pancreatic beta-cell SFU receptors, greater propensity for accumulation of active metabolites and greater penetration of pancreatic tissue.[18, 25-27] Glibenclamide can also increase insulin sensitivity greater than other SFUs, particularly when compared to gliclazide.[28] These factors combined with the long half-life, can lead to increased insulin release for longer periods after cessation of the medication, especially in decreased renal functions, as can be case in the elderly.[18, 25, 26]

Table 1 - Pharmacokinetic and Pharmacodynamic profile of Glibenclamide, Glipizide, Glimepiride and Gliclazide

Second Generation Sulfonylureas [14, 15, 19-23, 29-31]				
PK/PD Property	**Glibenclamide**	**Glimepiride**	**Glipizide**	**Gliclazide**
Duration of Action	<24h	24h	24h	24h
Volume of Distribution	9 to 10L	19.8 to 37.1L	10 to 11L	13 to 24L
Protein Binding	99%	99%	98 to 99%	85% to 99%
Metabolism	Hepatic, extensive	Hepatic, extensive	Hepatic, extensive	Hepatic, extensive
Absorption (Bioavailability)	Well absorbed, variable	100%	100%	80%
Half-life	10h	5h (+/-4.1h)	2 to 5h	8 to 12h
Time to Peak Concentration	2 to 4h	2 to 3h	1 to 3h	2 to 4h
Peak Response	2 to 3h	2 to 4h	2 to 3h	4 to 5h
Excretion	50% renal	60% renal	80% renal	80% renal
Dose adjustment in renal impairment	Yes, titrate appropriately			
Dose adjustment in hepatic impairment	Yes	Yes	Yes	Yes
Dose adjustment in Elderly	Yes, Initiate with conservative dose; for glibenclamide, do NOT titrate to maximum dose.			No [32, 33]
PK changes in Elderly	Slower elimination; higher volume of distribution.[24]	No significant differences in PK properties between younger and older adults.[19, 20, 22, 23]		Likely increase half-life and slower elimination.[30]

IV. Cost, Regulatory and Current NEML Availability Evaluation:

Table 2 below provides an overview of the cost per unit, per 30 units and estimated monthly cost of treatment with medications under review in US dollars. Glibenclamide and gliclazide prices are from the 2011 MSH International Drug Price Indicator Guide (MSH Guide).[17] Glipizide and glimepiride pricing is not available in the MSH guide, therefore, US market based pricing is listed from an online database, Lexi-Comp – this provides costs of medications as they pertain to US markets for comparison only and are not generalizable or indicative of global medication prices.[33] However, gliclazide is not registered in the US, therefore, no US market based pricing is available. It was not possible to compare gliclazide prices to UK or Australia as these systems operate on nationalized healthcare with negotiated prescription medication prices. US based Glibenclamide price is also listed for comparison. According to the MSH Guide, the monthly cost of gliclazide (with maximum daily dosing) at USD 2.83 is 3.3 times higher than the maximum daily dose price of glibenclamide at USD 0.85. However, it is important to note that these prices are based on the median buyer prices and may not reflect prices for procurement systems or patients. Table 2 below also shows the regulatory status of medications in the US (FDA), UK (MHRA) and Australia (TGA). [10-12]

Table 3 below evaluates the availability of glibenclamide, glipizide, glimepiride and gliclazide across 40 low and middle-income countries based on the NEML for each nation. The countries for this review were selected from the WHO website hosting NEMLs.[16] Most widely available second generation sulfonylurea was glibenclamide with a overall listing on 39 of the 40 NEMLs (97.5%); followed by gliclazide and glipizide, available on 50% and 27.5% of the NEMLs, respectively. The least available medication was glimepiride at 17.5%. It is logical that most nations would have glibenclamide as an option diabetes treatment given the medications listing on the WHO EML – a list that many nations use as a guide or a starting point to their own NEMLs. However, it was surprising that many nations had also added gliclazide (50%) and glipizide (27.5%) to their NEMLs. Furthermore, South Africa has gliclazid listed as an alternative to glibenclamide for the elderly and for patients with renal impairment.[32]

Table 2 - Comparative Cost Chart and Drug Approval by US, UK and Australian Regulatory Agencies

Medication (Name and Strength)	Cost per unit (USD)	Cost/30 tablets (USD)	Daily Maximum Dose[33]	Monthly cost based on maximum dosing (USD)	FDA Approved [10]	TGA Approved [12]	MHRA Approved [11]
International Drug Price Indicator Guide, 2011 (Management Science for Health) [17]							
Glibenclamide 5mg	0.0071	0.213	20mg/day	0.852	Yes	Yes	Yes
Glipizide 5mg*	N/A	N/A	40mg/day	N/A	Yes	Yes	Yes
Glimepiride 2mg*	N/A	N/A	8mg/day	N/A	Yes	Yes	Yes
Gliclazide 80mg	0.0236	0.708	320mg/day	2.832	No	Yes	Yes
Prices from Lexi-Comp Online (US market based prices) [33]							
Glibenclamide 5mg	1.580	47.4	20mg/day	189.6	Yes	Yes	Yes
Glipizide 5mg	0.2242	6.726	40mg/day	53.808	Yes	Yes	Yes
Glimepiride 2mg	0.211	6.33	8mg/day	25.32	Yes	Yes	Yes
Gliclazide 80mg	N/A	N/A	320mg/day	N/A	No	Yes	Yes

***MSH Guide does not provide median buyer prices for glipizide or glimepiride; ^Gliclazide is not registered in the US, therefore, no prices were compared.**

Table 3 - Sulfonylureas listed on selected NEMLs

#	Country	Glibenclamide	Gliclazide	Glipizide	Glimepiride
1	Argentina	Yes	No	Yes	No
2	Bangladesh	Yes	Yes	No	No
3	Bhutan	Yes	No	No	No
4	Central African Republic	Yes	Yes	No	No
5	China	Yes	No	Yes	No
6	Democratic Republic of Congo	Yes	No	No	No
7	Dominican Republic	Yes	No	No	No
8	Ecuador	Yes	No	No	No
9	Ethiopia	Yes	No	No	No
12	Fiji	Yes	No	Yes	No
10	Ghana	Yes	Yes	No	No
11	Georgia	Yes	No	No	No
13	India	Yes	No	No	No
14	Indonesia	Yes	No	Yes	No
15	Iran	Yes	Yes	Yes	No
16	Honduras	Yes	Yes	No	No
17	Kyrgyzstan	Yes	Yes	No	Yes
18	Lesotho	Yes	Yes	No	No
19	Malaysia	Yes	Yes	No	No
20	Malta	Yes	Yes	No	Yes
21	Montenegro	Yes	Yes	No	Yes
22	Morocco	Yes	Yes	No	Yes
23	Namibia	Yes	Yes	No	No
24	Nigeria	Yes	Yes	No	No
25	Oman	Yes	No	Yes	Yes
26	Pakistan	Yes	No	No	No
27	Paraguay	No	No	No	Yes
28	Republic of Moldova	Yes	No	No	No
29	Rwanda	Yes	Yes	No	No
30	Senegal	Yes	Yes	No	No
31	South Africa	Yes	Yes	No	No
32	Sri Lanka	Yes	No	No	No
33	Syrian Arab Republic	Yes	Yes	Yes	Yes
34	Thailand	Yes	Yes	Yes	No
35	Tunisia	Yes	Yes	Yes	Yes
36	Tonga	Yes	No	Yes	No
37	United Republic of Tanzania	Yes	Yes	Yes	No
38	Vanuatu	Yes	No	No	No
39	Yemen	Yes	No	No	No
40	Zimbabwe	Yes	No	No	No
Total # of surveyed countries with identified medications on the NEML		39 (97.5%)	20 (50%)	11 (27.5%)	7 (17.5%)

V. Comparative Safety and Efficacy Evaluation

For the treatment of diabetes, second generation sulfonylureas (SFUs) are one of the mainstays of therapy for most patients; SFUs primarily act by increasing release of insulin from the pancreas to relieve the hyperglycemia associated with diabetes.[34, 35] SFUs are generally well tolerated as a class; however, as discussed in Section III, pharmacokinetic differences within the agents can have significant clinical implications for patients.[36] The pharmacokinetic differences are amplified and particularly noticeable in the elderly patient.[36] One of the most common side effects of sulfonylureas is hypoglycemia, that if left untreated can lead to altered mental status, seizures, coma or death.[34, 37, 38] An estimated 20% of the patients on an SFU experience hypoglycemia within a 6-month period.[34, 39] Aging and pharmacokinetic changes predispose the elderly to experiencing such side effects at a higher rate.[36, 40] Therefore, for the purposes of evaluating safety of the three SFUs under review, the primary outcome of safety in the searched literature considered was hypoglycemia.

Efficacy of sulfonylureas has been evaluated using various criteria – primarily fasting and post-prandial plasma glucose levels and a reduction in HbA1c at the end of the treatment period. Therefore, for the purposes of evaluating efficacy of the four SFUs under review, the primary outcomes of efficacy in the searched literature considered were both plasma glucose levels (fasting and post-prandial) and HbA1c.

Appendix A below summarizes the literature review of trials, retrospective studies and systematic reviews that have evaluated both efficacy and safety of glibenclamide (glyburide), chlorpropamide and glipizide.

1. Evidence for Comparative Safety

Several studies have evaluated the comparative safety of SFUs in adults and specifically in the elderly (Appendix A). Four of the most pertinent studies are discussed here and summarized in Table 4 below.

A review of 57 cases of glibenclamide associated hypoglycemia by Asplund et al, showed that coma or altered mental status was the most common clinical presentation of serious hypoglycemia.[37] Twenty-four patients had long lasting (protracted) hypoglycemia lasting between 12 and 72 hours despite resuscitation attempts, resulting in 10 deaths.[37]

A retrospective, cohort study of more than 13,000 patients by Shorr et al, looked at risk of hypoglycemia with six different SFUs in the elderly, including glipizide and glibenclamide (glyburide).[25] The reviewers concluded that glyburide had the highest rate of hypoglycemia at 16.9 per 1000 person-years, compared to all other SFUs. When compared to glipizide, relative risk of severe hypoglycemia in glibenclamide patients was 1.9 (CI 1.2-2.9).[25] The authors also concluded that the physiological changes associated with increasing age such as declining renal

and hepatic function, as well as polypharmacy and concurrent illnesses additionally predispose the elderly to hypoglycemia; this predisposition is further compounded by use of glibenclamide.[25]

Another retrospective, cohort study of more than 33,000 patients in the UK by van Staa et al, compared risk of hypoglycemia with glibenclamide, gliclazide, chlorpropamide, tolbutamide and glipizide.[40] The study showed that the risk of hypoglycemia was higher with glibenclamide when compared to other SFUs.[40] The relative risks for hypoglycemia with gliclazide and glipizide compared with glibenclamide were 0.74 (CI 0.59-0.92) and 0.60 (CI 0.40-0.92), respectively.[40] The authors also concluded that elderly patients, older than 65 years, were at higher risk of experiencing hypoglycemia (annual risk of 2.0%) versus adults less than 65 years of age (annual risk of 1.4%) with a relative risk of 1.27 (CI 1.06-1.51).[40]

A 2007 meta-analysis of 21 studies compared glibenclamide (glyburide) with other hypoglycemic agents, including gliclazide, chlorpropamide and glipizide. [18] The study showed that there is an increased risk of hypoglycemia with glibenclamide by 52% than with other insulin secreting anti-diabetes therapies and 83% higher risk compared to other SFUs. [18] Table 5 below shows the relative risk of hypoglycemia associated with glibenclamide versus other SFUs from 8 studies as compiled by Gangji et al in their meta-analysis.[18] Of note, in two studies the relative risk of hypoglycemia with glipizide and gliclazide compared to glibenclamide was 2.96 (CI 0.32-27.74) and 2.23 (CI 1.08-4.59).[41, 42] Another study by Harrower et al, showed greater risk of hypoglycemia with glibenclamide compared to gliclazide with relative risk of 3.58 (CI 0.77-16.79). [43]

Table 4 - Four selected safety studies for glibenclamide associated hypoglycemia

Study	Design	Results/findings
Glibenclamide-associated hypoglycaemia: a report on 57 cases.[37] **Asplund K, et al. 1983**	Retrospective chart review of 57 cases to determine risk of hypoglycemia with glibenclamide in the elderly.	Coma or altered mental status was the most common clinical presentation. 22 patients responded to initial treatment, 24 had protracted hypoglycaemia of 12-72 h duration and 10 died. Fatal outcome was observed even with small doses of glibenclamide (2.5-5 mg/day). Contributing factors included impaired renal function, low food intake, diarrhoea, alcohol intake and interaction with other drugs. Glibenclamide, like the first-generation sulphonylureas, can cause serious, protracted and even fatal hypoglycaemic events.
Individual sulfonylureas and serious hypoglycemia in older people.[25] **Shorr RI, et al. 1996**	A retrospective cohort study of 13,963 Medicaid enrollees, aged 65 years or older, to determine risk of hypoglycemia with glibenclamide versus other SFUs.	The crude rate (per 1000 person-years) of serious hypoglycemia was highest in glyburide users, 16.6 (95% confidence interval [CI], 13.2 to 19.9). Users of tolbutamide, tolazamide, and glipizide had lower risks of serious hypoglycemia than users of chlorpropamide and glyburide. The adjusted relative risk of severe hypoglycemia among glyburide users, compared with glipizide users, was 1.9 (95% CI, 1.2 to 2.9).

		An increased risk of serious hypoglycemia associated with use of glyburide compared with glipizide occurred in all strata, including those defined by gender, race, nursing home residence, dose, and duration of use.
Rates of hypoglycemia in users of sulfonylureas.[40] **Van Staa, et al. 1997**	Retrospective, cohort study of 33,243 sulfonylurea patients to determine risk of hypoglycemia with glibenclamide versus other SFUs.	The rate and risk of hypoglycemia is higher for glibenclamide than for other sulfonylureas. The relative risks for hypoglycemia with gliclazide and glipizide compared with glibenclamide were 0.74 (CI0.59-0.92) and 0.60 (CI 0.40-0.92), respectively. Elderly patients, age greater than 65 years, are at increased risk of hypoglycemia than younger adults.
A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin.[18] **Gangji AS, et al. 2007**	A systematic review and meta-analysis comparing glyburide monotherapy with monotherapy using oral secretagogues or insulin.	Glyburide was associated with a 52% greater risk of experiencing at least one episode of hypoglycemia compared with other secretagogues (relative risk 1.52 [95% CI 1.21-1.92]) and with 83% greater risk compared with other sulfonylureas (RR 1.83 [95% CI 1.35-2.49]). Glyburide caused more hypoglycemia than other secretagogues and other sulfonylureas.

Table 5 - Relative risk of hypoglycemia with glibenclamide compared with other SFUs

Study	Sulfonylurea	Relative Risk [95% CI]
Baba, 1983 [41]	Gliclazide	2.23 [1.08 – 4.59]
Dills, 1996 [44]	Glimepiride	1.42 [0.94 – 2.13]
Draeger, 1996 [45]	Glimepiride	1.24 [0.90 – 1.71]
Haider, 1976 [46]	Chlorpropamide	5.26 [0.26 – 107.81]
Hamblin, 1970 [47]	Chlorpropamide	3.29 [0.72 – 15.05]
Harrower, 1994 [43]	Gliclazide	3.58 [0.77 – 16.79]
Rosenstock, 1993 [42]	Glipizide	2.96 [0.32 – 27.74]
United Kingdom Prospective Diabetes Study, 1995 [48]	Chlorpropamide	2.39 [1.78 – 3.20]
CI – Confidence Interval; Data is adapted from Gangji AS, et al. [18]		

Furthermore, Lexi-Comp, an online clinical pharmacy database in the US also recommends against the use of glibenclamide in the elderly, citing: “Glyburide is not a drug of choice for the elderly because of its association with severe hypoglycemia. Rapid and prolonged hypoglycemia (>12 hours) despite hypertonic glucose injections has been reported; age, hepatic, and renal impairment are independent risk factors for hypoglycemia; dosage titration should be made at weekly intervals.” And warns against titration of dose to maximum doses recommended for adults.[14] The British National Formulary also makes a similar recommendation against glibenclamide and recommends use of shorter-acting SFUs, such as gliclazide.[13]

Finally, according to the American Geriatrics Society’s Beers criteria, a project aimed at using comprehensive, systematic review and grading of the evidence on drug-related problems and adverse drug events (ADEs) to promote safe use of medications in older adults, glibenclamide

should be avoided in the elderly due to greater risk of severe prolonged hypoglycemia. The quality of evidence for this is high and the strength of the recommendation is strong. [49]

2. Evidence for Comparative Efficacy

Several studies have evaluated the comparative efficacy of glibenclamide against other second generation SFUs. Two studies comparing efficacy of glibenclamide versus gliclazide measured with reduction in fasting and post-prandial plasma glucose levels and a reduction in HbA1c, showed no differences between the two treatments. [28, 50] A placebo controlled study to determine efficacy of gliclazide showed significant reduction with SFU treatment in plasma glucose levels and HbA1c.[51]

Three clinical studies compared efficacy of glibenclamide and glimepiride showed similar results for reductions in plasma glucose levels or HbA1c, indicating similar efficacy. [45, 52, 53] A literature review considering 1-year trials comparing safety and efficacy of glimepiride with other SFUs found no differences in efficacy, while proving glimepiride is safer with fewer hypoglycemic events.[54]

Three clinical studies that compared efficacy of glibenclamide and glipizide showed similar results for reductions in plasma glucose levels or HbA1c, indicating similar efficacy. [53, 55, 56]

Finally, the meta-analysis by Gangji et al, showed that based on HbA1c results, compared to other SFUs, including gliclazide, glimepiride and glipizide, glibenclamide did not have an increased efficacy in treatment of diabetes.[18]

3. Summary of Comparative Safety and Efficacy Evidence

Compared with other sulfonylureas, glyburide has been associated with an increased risk of severe hypoglycemia, especially in the elderly. [57, 58] Systematic reviews discussed above provide data that show the increased relative risk of hypoglycemia and the resulting harm with use of glibenclamide versus any of the other second generation SFUs, particularly gliclazide and glipizide. The data unequivocally recommends against the use of glibenclamide in elderly patients.[59] In fact, South Africa treatment guidelines have listed gliclazid as an alternative to glibenclamide for the treatment of elderly and for patients with renal impairment.[32]

Efficacy evidence has proven that there is no associated benefit (lower HbA1c) with the use of glibenclamide when compared with other second generation SFUs.[18] Evidence fails to identify significant differences in the efficacy between second generation SFUs.[18]

VI. Summary and Recommendations

This report has compiled and analyzed comparative evidence for safety and efficacy of second generation SFUs with a focus on glibenclamide (currently on EML), glimepiride, glipizide and gliclazide. The evidence shows that glibenclamide is not a safe medication for use in the elderly (patients older than 60 years of age). The evidence also shows that all four of these agents are equally effective in reducing HbA1c.

For potential alternatives to glibenclamide, the availability survey of 40 LMICs based NEML review shows that availability is highest for gliclazide (50%) and glipizide (27.5%). Based on the cost in Table 2 above, it is possible to compare costs of glibenclamide and gliclazide in international arena. According to the 2011 MSH International Drug Price Indicator Guide, the potential monthly cost of gliclazide (USD 2.83) is 3.3 times higher than glibenclamide (USD 0.85).

Based on a review of safety, efficacy, cost and NEML availability of glibenclamide, gliclazide, glipizide and glimepiride, the recommendations are as follow:

3. Glibenclamide 2.5mg and 5mg tablets should remain on the EML with age restriction recommending against use in patients older than 6o years of age.
4. Gliclazide 80mg tablet should be added to the EML for use in the elderly with type 2 diabetes, with a square box designation so as to indicate that other second general sulfonylureas (other than glibenclamide) are an acceptable alternative.

Table 6 - Gliclazide dosing information

Medication	Initial Dose	Maximum Dose	Comments/Monitoring
Gliclazide 80mg tablet [13, 32, 33]	40-80 mg twice daily	320 mg per day Dosage of ≥160 mg should be divided into 2 equal parts for twice-daily administration	Maintain adequate caloric intake. Take with breakfast. Titrate based on plasma glucose levels/clinical response. Educate patient and monitor for signs and symptoms of hypoglycemia. All sulfonylureas have an increased risk of hypoglycemia in the elderly patients.

Appendix A – Summary of Literature Review: Safety and Efficacy Evidence Table

Study	Design/Population	Medications	Objectives	Results/findings
Glibenclamide-associated hypoglycaemia: a report on 57 cases.[37] **Asplund K, et al. 1983**	Retrospective chart review, 51 cases.	Glibenclamide	To determine incidence of hypoglycemic events in the elderly with use of glibenclamide	Median age of the patients with hypoglycaemia was 75 years and 21% were 85 years or above. The median daily dose of glibenclamide prescribed was 10 mg both in the hypoglycaemic cases and in the prescription sample. Coma or disturbed consciousness was the most common clinical presentation. 22 patients responded to initial treatment, 24 had protracted hypoglycaemia of 12-72 h duration and 10 died. Fatal outcome was observed even with small doses of glibenclamide (2.5-5 mg/day). Contributing factors included impaired renal function, low food intake, diarrhoea, alcohol intake and interaction with other drugs. Glibenclamide, like the first-generation sulphonylureas, can cause serious, protracted and even fatal hypoglycaemic events.
Diabetes control in the elderly: a randomized, comparative study of glyburide versus glipizide in non-insulin-dependent diabetes mellitus.[42] **Rosenstock J, et al. 1993**	Randomized study. 145 patients aged > or = 65 years with NIDDM.	Glipizide and Glyburide (glibenclamide) 139 patients randomized to glyburide, 1.25 or 2.5 mg/day, or glipizide, 2.5 or 5 mg/day. For 4 months	To compare the efficacy and safety of glyburide and glipizide in elderly patients with well-controlled non-insulin-dependent diabetes mellitus (NIDDM)	Hypoglycemia was defined as fasting plasma glucose of < 3.3 mmol/L (60 mg/dl) or a random plasma glucose of < 2.8 mmol/L (50 mg/dl), with associated signs and symptoms. Most patients in both the glyburide and glipizide groups achieved satisfactory glycemic control. No significant differences between groups in fasting plasma glucose or hemoglobin A1c levels at any time. Both regimens were well tolerated and were associated with a similarly low incidence of hypoglycemia. It was concluded that both glyburide and glipizide are suitable for the treatment of NIDDM in properly selected elderly patients.
Pharmacokinetics and pharmacodynamics of glyburide in young and elderly nondiabetic	Pharmacokinetics and Pharmacodynamics study Non-diabetic, 20 elderly (mean +/- S.D. age, 65.7 +/- 5.3	Glibenclamide 5mg, single dose	To determine PK and PD effects of glyburide in young and elderly patients	Compared with the young subjects, the elderly subjects had slower glyburide absorption and smaller area under the plasma concentration-time curve from zero to four hours (AUC0-4). The elderly subjects also had a lower glyburide elimination rate constant and higher volume of distribution and a 52% higher free fraction.

adults.[24] **Schwinghammer TL, et al. 1991**	years) male (n = 10) and female (n = 10) volunteers and 15 young (22.3 +/- 4.5 years) male volunteers.			The aging process appears to affect the pharmacokinetics and pharmacodynamics of glyburide.
Glipizide pharmacokinetics: effects of age, diabetes, and multiple dosing. [23] **Kradjan WA, et al. 1989**	Pharmacokinetics and Pharmacodynamics study Ten healthy young men (under age 25), ten healthy older men (over age 65) and 15 older diabetic men	Glipizide 5mg	To determine the effects of aging, the presence of NIDDM, and multiple dosing on the pharmacokinetics of glipizide	The mean values for Tmax (range 2.0-2.5 hours), Cmax (385-465 micrograms/l), and t1/2 (4.0-4.2 hours) were not significantly different in the three populations after single doses of glipizide. AUC, Cl, Vss and V area were not significantly different in the three populations or at steady state, but there was a trend for AUC to be smaller and each of the other parameters to be increased in the older diabetics. The young subjects had a significantly higher free fraction (0.83%) than either of the two elderly groups (0.55-0.64%), but CI did not differ between groups. Age, diabetes, and multiple dosing appear to have little effect on the pharmacokinetics of glipizide and should have little influence on the clinical response to glipizide.
Gliclazide: a preliminary review of its pharmacodynamics properties and therapeutic efficacy in diabetes mellitus.[31] **Holmes B, et al. 1984**	Summary of Pharmacokinetics and Pharmacodynamics studies	Gliclazide	To summarize pharmacokinetic and pharmacodynamics properties of gliclazide.	Gliclazide is well absorbed orally with a variable peak plasma concentration time of 0.4 to 4.8 hours. Volume of distribution is low ranging from 15.9L to 17.4L indicating limited tissue distribution. Plasma protein binding is high ranging from 85 to 97%. Gliclazide is both metabolized and renally eliminated. Half-life is variable in males and females around 8 and 11 hours, respectively.
Glipizide pharmacokinetics in young and elderly volunteers.[22] **Kobayashi KA, et al. 1988**	Pharmacokinetics and Pharmacodynamics study Ten healthy young men (24.9 +/- 1.9 years of age) and 10 healthy older men (74.4 +/- 7.9 years of age)	Glipizide 5mg	To determine the effects of aging on the pharmacokinetics of glipizide	The mean values for young and older subjects for time to peak concentration (2.1 versus 2.5 hours), peak concentrations (465 versus 399 micrograms/mL), elimination half-life (4.2 versus 4.0 hours), clearance (38.8 versus 38.1 mL/min), and distribution volume at steady state (12.5 versus 14.3 L) were not significant. Two older individuals had a prolonged time to peak concentration (six to eight hours). There is no significant difference in the pharmacokinetics of glipizide between young and older participants.
Glibenclamide induced prolonged hypoglycaemia.[60]	Retrospective chart review, 13 patients, 68 years and older	Glibenclamide	To determine association between prolonged	Prolonged hypoglycemia - serum glucose levels of 50 mg/dl and less, for more than 12 h in spite of treatment with periodic injections of hypertonic glucose - secondary to treatment with glibenclamide.

Sonnenblick M, et al. 1986			hypoglycemia and use of glibenclamide in elderly patients.	The mean daily dose of glibenclamide was 6.7 mg. In nine patients, the hypoglycemia developed within 7 days of treatment. In two patients the tendency to hypoglycemia lasted for more than 60 h in spite of continuous infusion of 5% or 10% glucose. Old age is a crucial predisposing factor. Contributing factors were renal failure and congestive heart disease. Glibenclamide should be used with care in the elderly and in patients with renal or cardiac failure.
Benefits and risks with glyburide and glipizide in elderly NIDDM patients.[55] **Brodows RG, et al. 1992**	Randomized crossover trial, 21 elderly patients (mean age = 70years)	Glyburide or Glipizide For 8 weeks	To compare the efficacy, benefits, and risks of glyburide and glipizide in elderly patients with non-insulin-dependent diabetes mellitus (NIDDM).	Glipizide (11.9 mg) and glyburide (8.4 mg) produced similar fasting and postprandial plasma glucose and HbA1c concentrations. A significantly higher incidence of SMBG readings less than 4.5 mM was attributed to glyburide (11%) than glipizide (7%), $p<0.05$. Both treatments proved effective for glycemic control. Both second-generation sulfonylureas are associated with a significant risk of hypoglycemia in elderly NIDDM patients.
Hypoglycemia in hospitalized patients treated with sulfonylureas.[58] **Deusenberry CM, et al. 2012**	Nested case-control study, adults who received a sulfonylurea during hospitalization and experienced at least one episode of hypoglycemia.	Glyburide, glimepiride or glipizide	To identify the incidence of and risk factors associated with hypoglycemia in hospitalized patients taking sulfonylureas.	Hypoglycemia, defined as a blood glucose level less than 70 mg/dl. 19% of patients who received a sulfonylurea experienced at least one episode of hypoglycemia: 22% received glyburide, 19% received glimepiride, and 16% received glipizide. 65 years or older (odds ratio [OR] 3.07, $p < 0.001$) was a predictor of hypoglycemia. Cases were less likely than controls to receive glipizide (OR 0.44, p=0.005). Hospitalized patients at increased risk for sulfonylurea-related hypoglycemia were those aged 65 years or older and those with a GFR of 30 ml/minute/1.73 m(2) or lower. Sulfonylureas should be avoided or used with caution in these patients.
A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin.[18]	A systematic Review; parallel, randomized, controlled trials in people with type 2 diabetes comparing glyburide monotherapy with monotherapy using	Sulfonylureas	To determine if glyburide causes more hypoglycemia and cardiovascular events than other secretagogues or insulin	Glyburide was associated with a 52% greater risk of experiencing at least one episode of hypoglycemia compared with other secretagogues (relative risk 1.52 [95% CI 1.21-1.92]) and with 83% greater risk compared with other sulfonylureas (RR 1.83 [95% CI 1.35-2.49]). Glyburide was not associated with an increased risk of cardiovascular events (0.84 [0.56-1.26]), death (0.87 [0.70-1.07]), or end-of-trial weight (weighted mean difference 1.69 kg [95% CI -0.41 to 3.80]) compared with other

Gangji AS, et al. 2007	secretagogues or insulin were selected.			secretagogues. Glyburide caused more hypoglycemia than other secretagogues and other sulfonylureas.
Drug-induced hypoglycemia. A review of 1418 cases. [61] **Seltzer HS. 1989**	Retrospective case review of 1,418 cases.	Sulfonylureas (chlorpropamide and glyburide)	To determine which medications are responsible for causing hypoglycemia.	Sulfonylureas (especially chlorpropamide and glyburide), either alone or with a second hypoglycemic or potentiating agent, account for 63% of all cases of hypoglycemia. 86% of the hypoglycemia cases with sulfonylurea therapy were patients older than 50 years. An estimated 80% of the hypoglycemia cases omitted one or more meals.
Comparative tolerability of sulphonylureas in diabetes mellitus.[59] **Harrower AD. 2000**	Systematic review	Sulfonylureas	To determine comparative tolerability of sulfonylureas	The relative risk for recorded hypoglycemia showed an increased risk for glibenclamide-treated patients compared with other sulfonylureas (adjusted relative risk versus glibenclamide: 0.74, 0.75, 0.60 for gliclazide, tolbutamide and glipizide, respectively). Glibenclamide and chlorpropamide should be avoided in elderly patients and those with impaired renal function.
Rates of hypoglycemia in users of sulfonylureas.[40] **Van Staa, et al. 1997**	Retrospecitve, cohort study of 33,243 sulfonylurea patietns	Sufonylureas	To identify the demographic and clinical characteristics of sulfonylurea users. To assess the risk of hypoglycemia in patients treated with sulfonylureas in clinical practice, and to characterize the risk in relation to the different drugs used.	A diagnosis of hypoglycemia during sulfonylurea therapy was recorded in 605 people over 34,052 person-years of sulfonylurea therapy, which converted into an annual risk of 1.8%. The risk in glibenclamide users was higher than in users of other types of sulfonylureas uses. Duration of therapy, concomitant use of insulin, sulfonylurea-potentiating or antagonizing and concomitant use of beta-blockers were predictive of the risk of developing hypoglycemia. The rate of hypoglycemia is higher for glibenclamide than for other sulfonylureas.
Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents.[39] **Jennings AM, et al. 1989**	Retrospective chart review. Older adults (age 40 to 65 years), on oral hypoglycemic agents, 203 patients.	Oral hypoglycemic agents, including sulfonylureas	To determine prevalence and causes of hypoglycemia in patients receiving oral hypoglycemic.	Hypoglycemic symptoms were experienced by 41 of 203 (20.2%) patients treated with sulfonylureas but in none of the 16 patients treated with metformin alone. Hypoglycemic symptoms were experienced at least monthly in 5.9% and less frequently in 14.3% of patients. The prevalence of hypoglycemic symptoms was significantly higher in patients treated with glyburide than in patients treated with gliclazide ($P<0.01$) or chlorpropamide ($P<0.05$).

				The prevalence of symptoms was higher in patients taking medications in addition to OHAs (P < 0.01). Ten (24%) of the patients who experienced hypoglycemic symptoms were taking drugs that may potentiate sulfonylureas.
The relatively frequent incidence of severe sulfonylurea-induced hypoglycemia in the last 25 years in Switzerland. Results of 2 surveys in Switzerland in 1969 and 1984. [62] **Berger W, et al. 1986**	Retrospective chart review in emergency ward patients with severe hypoglycemia over two periods. Period 1, n=78; period 2, n=116.	Sulfonylureas	To determine the incidence of sulfonylurea induced severe hypoglycemia.	The risk of hypoglycemia is significantly higher with glibenclamide and chlorpropamide than with glibornuride and tolbutamide. Advanced age proved to be a risk factor in HE: 77% of patients with HE were over 69 years of age, whereas only 50% of all diabetics treated with sulfonylurea preparations were in this age group. Further risk factors were impaired renal function (21%) and possible drug interactions (27%).
Long-term comparative trial of glibenclamide and chlorpropamide in diet-failed, maturity-onset diabetics.[63] **Clarke BF, et al. 1975**	Randomized, prospective, long-term (2 year) study. 321, diet-failed, non-obese, diabetic patients, 40 years and older (94 patients over 60 years).	Glibenclamide Chlorpropamide	To compare the clinical effectiveness of glibenclamide with chlorpropamide.	The primary failure-rate in the chlorpropamide group was less ($p<0.05$) Greater number of patients were on chlorpropamide at the end of two years than on glibenclamide ($p<0.01$). Secondary failures rates between treatment groups was not significant. Using plasma glucose levels and weight, the efficacy of the treatment at the of 2 years was similar in both groups. Hypoglycaemic episodes were more common (total 8) and severe (4 patients went into a coma) in the glibenclamide group than the chlorpropamide group (total 3, none severe).
Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience.[64] **Massi-Benedetti M. 2003**	Literature review	Glimepiride	To provide a comprehensive summary of available data on the pharmacology, pharmacokinetics, efficacy, and safety profile of glimepiride in the treatment of type 2 diabetes.	In clinical studies, glimepiride was generally associated with a lower risk of hypoglycemia and less weight gain than other SUs. Results of studies suggest that glimepiride can be used in older patients and those with renal compromise. There is evidence that glimepiride preserves myocardial preconditioning, a protective mechanism that limits damage in the event of an ischemic event. Glimepiride can be used in combination with other oral antidiabetic agents or insulin to optimize glycemic control. Based on the evidence, glimepiride is an effective and well-tolerated once-daily antidiabetic drug.
Effects of glimepiride	Open, uncontrolled	Glimepiride	To examine the efficacy	HbA1c was reduced from 8.4% at baseline to 7.1% after 4 months and 6.9%

on HbA(1c) and body weight in Type 2 diabetes: results of a 1.5-year follow-up study.[65] **Weitgasser R, et al. 2003**	surveillance study, 284 patients for follow-up.	Patients received 0.5 to >4 mg glimepiride once daily for 1.5 years.	and safety of glimepiride.	after 1 and 1.5 years (P<0.0001). Treatment with glimepiride also resulted in significant and stable weight loss relative to baseline, with the exception of patients with a body mass index of <25 kg/m(2). Once daily glimepiride provides effective glycemic control, and may have advantages over other sulfonylureas, because it exhibits weight neutralizing/reducing effects in patients with Type 2 diabetes
Glimepiride. A review of its use in the management of type 2 diabetes mellitus.[54] **Langtry HD, et al. 1998**	Literature review	Glimepiride	To provide a summary of efficacy and safety of glimepiride use is type 2 diabetes patients.	Glimepiride has fewer and less severe effects on cardiovascular variables than glibenclamide (glyburide). Pharmacokinetics are mainly unaltered in elderly patients or those with renal or liver disease. Glimepiride was similar in efficacy to glibenclamide and glipizide in 1-year studies. Glimepiride appears to reduce blood glucose more rapidly than glipizide over the first few weeks of treatment. Glimepiride and gliclazide were compared in patients with good glycemic control at baseline in a 14-week study that noted no differences between their effects. Pooled clinical trial data suggest that glimepiride may have a lower incidence of hypoglycemia than glibenclamide, particularly in the first month of treatment.
The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan.[66] **The Glimepiride in Ramadan (GLIRA) Study Group. 2005**	Randomized controlled trial. 332 patients, fasting for one month.	Glimepiride	To determine efficacy and safety of glimepiride use in type 2 diabetic patients who observer Ramadan.	HbA_{1c} values (% ± SD) decreased during the study period. Reported hypoglycemic events ranged from 25 (in 13 subjects) in pre-Ramadan to 15 (in 11 subjects) during Ramadan and 8 (in 8 subjects) in post-Ramadan periods. Results show that the efficacy and safety of glimepiride in type 2 diabetic patients is not altered during the month-long daylight fast of Ramadan. During Ramadan the incidence of hypoglycemic episodes was 3% in newly diagnosed patients and 3.7% in already-treated patients. These figures were similar to the pre- and post-Ramadan periods.
A prospective trial of risk factors for sulfonylurea-induced hypoglycemia in type 2 diabetes mellitus.[34]	A prospective, randomized, double-blind clinical trial. 52 sulfonylurea-treated patients with type 2 diabetes with a mean age of 65.1 years.	Glyburide or Glipizide 1 week of placebo, 1 week of 10 mg and 1 week of 20 mg of the assigned	To evaluate the hypoglycemic effects of maximum doses of once-daily second-generation sulfonylureas administered to fasting	No hypoglycemia was observed during 156 fasting studies. Plasma glucose level was decreased [88 mg/dL] for a 20-mg dose of glyburide vs [150 mg/dL] for placebo; [105 mg/dL] for a 20-mg dose of glipizide vs [157 mg/dL] for placebo. Plasma glucose parameters did not differ between the 2 sulfonylureas

Burge MR, et al. 1998		sulfonylurea.	elderly patients.	Fasting was well tolerated among these elderly patients with type 2 diabetes treated with sulfonylureas. Older age should not be considered a contraindication to sulfonylurea treatment for diabetes.
Individual sulfonylureas and serious hypoglycemia in older people.[25] **Shorr RI, et al. 1996**	A retrospective cohort study. A total of 13,963 Medicaid enrollees, aged 65 years or older, who were prescribed one of six sulfonylureas from 1985 to 1989.	Sulfonylureas	To compare the risk of serious hypoglycemia associated with the use of individual sulfonylureas in older people.	The crude rate (per 1000 person-years) of serious hypoglycemia was highest in glyburide users, 16.6 (95% confidence interval [CI], 13.2 to 19.9 and lowest among users of tolbutamide, 3.5 (95% CI, 1.2 to 5.9). Users of tolbutamide, tolazamide, and glipizide had lower risks of serious hypoglycemia than users of chlorpropamide, whereas the risk of serious hypoglycemia among glyburide users did not differ from that of chlorpropamide users. The adjusted relative risk of severe hypoglycemia among glyburide users, compared with glipizide users, was 1.9 (95% CI, 1.2 to 2.9). An increased risk of serious hypoglycemia associated with use of glyburide compared with glipizide occurred in all strata, including those defined by gender, race, nursing home residence, dose, and duration of use. These data indicate that glipizide is less associated with hypoglycemia than is glyburide.
Comparison of gliclazide and glibenclamide treatment in non-insulin-dependent diabetes.[41] **Baba S, et al. 1983**	Multicenter, double blind, randomized study in Japan 289 type 2 diabetes patients (113 were 60 years and older)	Gliclazide and Glibenclamide	To assess efficacy and safety of gliclazide compared to glibenclamide	Hypoglycemia incidence was significantly lower in gliclazide group versus glibenclamide group (7% versus 15%). No significant differences in efficacy for reduction of blood glucose levels with either treatment.
A clinical comparison between glipizide and glibenclamide in the treatment of maturity onset diabetes: A controlled double-blind cross-over study.[67] **Frederiksen PK, et al. 1982**	Randomized, controlled, double-blind, cross-over study in 38 patients.	Glipizide and Glibenclamide	To compare efficacy and tolerability of glipizide and glibenclamide	The increase in postprandial blood glucose levels was found to be significantly lower with glipizide treatment than with glibenclamide treatment. The fasting blood glucose was significantly lower during glibenclamide treatment. No differences were found in the other parameters tested (weight, ECG, serum cholesterol, serum triglyceride). Hypoglycaemic reactions were the only side effects. Six episodes occurred in each treatment group. Eleven episodes were mild. One episode with moderately severe hypoglycaemia occurred with glibenclamide.
Comparative efficacy and potency of long-	Randomized prospective trial; 18	Glibenclamide and Glipizide, over a	To compare the effectiveness and	Similar doses of glipizide (11 mg/day) or glyburide (10 mg/day) resulted in comparable reduction of FPG and hemoglobin A1c and increase in first phase

term therapy with glipizide or glyburide in patients with type 2 diabetes mellitus.[68] **Kitabchi AE, et al. 2000**	patients with type 2 diabetes mellitus (DM2)	15-month period in (9 on glibenclamide and 9 on glipizide).	relative potency of glipizide and glyburide.	insulin response to intravenous glucose tolerance testing. There was greater reduction in FPG and 2-hour postprandial plasma glucose with glipizide than with glyburide in 6 months. This long-term study demonstrated that glipizide and glyburide are equipotent at similar doses in controlling hyperglycemia in DM2.
Long-term beneficial effects of glipizide treatment on glucose tolerance in subjects with impaired glucose tolerance.[69] **Eriksson JG, et al. 2006**	Randomized, placebo-controlled trial; 37 patients with type 2 diabetes.	Glipizide 2.5mg or placebo for 18 months	To assess the efficacy and long-term effects of glipizide treatment on glucose and insulin metabolism in individuals with impaired glucose tolerance (IGT).	Fasting insulin improved in the glipizide group (P = 0.04 and 0.02 respectively) as well as HDL cholesterol (P = 0.05) compared with placebo group after 6 months. At 18 months, both fasting and 2 h glucose concentrations were significantly lower in the glipizide group compared with the placebo group (P = 0.04 and 0.03 respectively). The prevalence of type 2 diabetes was 29.4% in the placebo group and 5.9% in the glipizide group at 18 months. This equals an 80% relative risk reduction in the active treatment group.
Efficacy of glimepiride in Japanese type 2 diabetic subjects. [53] **Inukai K, et al. 2005**	Randomized, controlled trial, 172 Japanese type 2 diabetic patients	Glimepiride, gliclazide or glibenclamide	To determine efficacy of glimepiride compared to gliclazide and glibenclamide.	After 6 months, glycemic control (HbA1C and fasting plasma glucose) had not changed significantly in either treatment group. Showed equal efficacy for the three medications in controlling HbA1C.
Muslims with non-insulin dependent diabetes fasting during Ramadan: treatment with glibenclamide.[70] **Belkhadir J, et al. 1993**	Cohort, randomized and non-randomized groups of 591 diabetic patients	Glibenclamide	To compare the efficacy of two glibenclamide regimens in patients with non-insulin dependent diabetes who were fasting during Ramadan and regular glibenclamide treatment in the non-fasting group.	At the end of Ramadan there were no significant differences between the groups in fructosamine concentration (400 mumol/l in controls and 381 mumol/l and 376 mumol/l in the fasting groups); percentage of glycated haemoglobin (14.7%, 14.0%, and 13.6%); or number of hypoglycaemic events during Ramadan (11, 14, and 10). Glibenclamide is effective and safe for patients with non-insulin dependent diabetes who fast during Ramadan.
Glimepiride, a new once-daily sulfonylurea. A double-blind placebo-controlled study of NIDDM patients.[71] **Rosenstock J, et al.**	Multicenter randomized double-blind placebo-controlled fixed-dose study. 416, type 2 diabetic patients.	Glimepiride or placebo for 14 weeks Course of placebo or glimepiride 8 mg daily, 4 mg twice daily, 16 mg	To compare the efficacy and safety of two daily doses of the new sulfonylurea, glimepiride, each as a once-daily dose or in two divided doses, in patients with NIDDM.	The placebo group's FPG value increased from 13.0 mmol/l at baseline to 14.5 mmol/l at the last evaluation endpoint (P < or = 0.001). FPG values in the four glimepiride groups decreased from a range of 12.4-12.9 mmol/l at baseline to a range of 8.6-9.8 mmol/l at endpoint (P < or = 0.001, within-group change from baseline; P < or = 0.001, between-group change [vs. placebo] from baseline).

1996		daily, or 8 mg twice daily.		In the placebo group, the HbA1c value increased from 7.7% at baseline to 9.7% at endpoint (P < or = 0.001), whereas HbA1c values for the glimepiride groups were 7.9-8.1% at baseline and 7.4-7.6% at endpoint (P < or = 0.001, within-group change from baseline; P < or = 0.001, between-group change from baseline). Glimepiride is an effective oral glucose-lowering agent.
Long-Term Randomized Placebo -Controlled Double-Blind Therapeutic Comparison of Glipizide and Glyburide. [56] **Birkeland, et al. 1994**	Prospective, randomized, double-blind, placebo-controlled study on 46 NIDDM patients comparing fasting levels and test-meal responses of glucose and insulin during 15 months of follow-up.	Glyburide and Glipizide	To examine the long-term (15 months) effects on glycemic control and insulin secretion of glipizide and glyburide treatment in patients with non-insulin-dependent diabetes mellitus (NIDDM).	A comparable reduction in HbA1c levels by both agents versus placebo was observed throughout the study period, but after a marked initial reduction in both sulfonylurea groups, all three groups showed gradually increasing HbA1c levels. However, both glipizide and glyburide achieved and maintained lowered postprandial glucose levels and increased fasting and postprandial insulin levels compared with placebo. Both glipizide and glyburide may achieve and maintain glycemic reduction and stimulation of insulin secretion during long-term treatment.
Clinical trials with glimepiride.[52] **Clark CM, et al. 1998**	Review of 21 placebo-controlled, active-controlled or noncomparative studies with 6500 patients (4220 of treated with glimepiride)	Glimepiride compared to placebo or other sulfonylureas (glyburide, gliclazide and glipizide)	To review efficacy of glimepiride in treatment of diabetes versus placebo and other second generation SFUs.	Glimepiride is equally effective as glyburide and glipizide. At lower doses, glimepiride may have a superior safety profile compared to glyburide, glipizide and gliclazide.
Long-term treatment of type 2 diabetic patients with the new oral antidiabetic agent glimepiride (Amaryl): a double-blind comparison with glibenclamide.[45] **Draeger KE, et al. 1996**	Prospective, double-blind trial, randomized active-controlled trial 1444 type 2 diabetic patients, with median age 60.2 years	Glimepiride (1-8mg) and Glibenclamide (2.5 – 20mg)	To compare efficacy and safety of glimepiride compared to glibenclamide	Mean HbA1c and mean fasting blood glucose were not statistically or clinically significant between the two agents (8.4% and 174 mg/dl (9.7 mmol/l) for glimepiride and 8.3% and 168 mg/dl (9.3 mmol/l) for glibenclamide) Both treatment groups showed an equivalent safety profile. Fewer hypoglycemic reactions occurred with glimepiride than with glibenclamide (105 versus 150 episodes). Long-term follow-up of 457 patients showed that glimepiride (1-8 mg) once daily is as efficacious as glibenclamide (2.5-20.0 mg).
Gliclazide. An update of its pharmacological properties and therapeutic efficacy in non-insulin-	Drug review	Gliclazide	To present pharmacokinetic, efficacy and safety information on gliclazide.	Gliclazide can control blood glucose levels in 62 to 97% of patients. Gliclazide can reduce fasting glucose levels by 12 to 62.1% and postprandial glucose levels by 18 to 26.7%. Gliclazide is associated with a low incidence of hypoglycemia.

dependent diabetes mellitus.[30] **Palmer KJ, et al. 1993**				
Efficacy of gliclazide in comparison with other sulphonylureas in the treatment of NIDDM.[50] **Harrower, AD. 1991**	Review of three clinical studies: Study 1: 224 diabetic patients, multicenter, randomized, 3 months Study 2: 112 diabetic patients, randomized, five cohorts, one year Study 3: 248 diabetic patients, randomized, three cohorts, five years	Gliclazide Other SFUs	To determine efficacy and safety of gliclazide compared with other SFUs	Study 1: Gliclazide is able to achieve adequate blood glucose control in 65% of the patients within three months. Gliclazide also improved glucose control in 49% of patients who had failed other anti-diabetic medications. Study 2: Study drugs (n): chlorpropamide (21), glipizide (24), gliquidone (22), gliclazide (22) and glibenclamide (23). Similar efficacy between glibenclamide and gliclazide was observed at 74% and 80% patients observing decreases in HbA1c. Gliclazide produced better HbA1c control compared to chlorpropamide (17%, p=0.01), gliquidone (40%, p=0.038) and glipizide (40%, p=0.01). Study 3: Compared to glipizide (25.6%) and glibenclamide (17.9%), gliclazide (7%), had the lowest rate of secondary failure to SFU therapy. The failure rate was significant between gliclazide and glipizide ($p<0.05$), however, not significant between gliclazide and glibenclamide ($p<0.1$). The incidence of hypoglycemia was significantly higher with glibenclamide versus gliclazide ($p<0.05$). Gliclazide efficacy is similar to other SFUs, particularly glibenclamide and glipizide. Gliclazide causes less hypoglycemia than glibenclamide.
Glibenclamide vs gliclazide in type 2 diabetes of the elderly.[28] **Tessier, D. et al. 1994**	Randomized, double blind 22 elderly patients with diabetes	Glibenclamide and Gliclazide	To compare the efficacy and safety of glibenclamide and gliclazide in elderly patients.	Similar efficacy of the two agents using oral glucose tolerance test and HbA1c was observed ($p >0.05$ for both tests) at 6 months. Hypoglycemic event rate was significantly higher with glibenclamide than with gliclazide: 17 vs 4 ($p < 0.01$). Insulin sensitivity index (ml kg-1 min-1 pmol-1 x 100) was increased significantly by glibenclamide but not gliclazide (glibenclamide: 0.284 +/- 0.116 (baseline) vs 0.518 +/- 0.102 (6 months) ($p < 0.05$), gliclazide: 0.260 +/- 0.048 (baseline) vs 0.358 +/- 0.048 (6 months) ($p > 0.05$)). Glycaemic control was equivalent with the two drugs but the incidence of hypoglycemic events was significantly greater with glibenclamide; likely due to glibenclamide's ability to increase insulin sensitivity to a greater degree.
The action of gliclazide on insulin secretion and insulin sensitivity in non-obese non-insulin	Placebo controlled, double-blind, cross-over study. 18 diabetic patients, mean age 57 years.	Gliclazide or Placebo	To determine efficacy of gliclazide in reducing plasma glucose and HbA1c compared to placebo.	After gliclazide therapy, fasting and 2 hour post-oral glucose tolerance test plasma glucose significantly decreased ($p< 0.005$) and plasma insulin was significantly increased ($p<0.05$) while fasting plasma insulin remained unchanged ($p>0.1$).

dependent diabetic patients.[51] **Chang TC, et al. 1990**	HbAlc decreased significantly with gliclazide therapy (6.6 vs. 7.6%, $p<0.005$).

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