Drug Programs Branch Bulletin

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Diabetes – A Treatment Overview

While the incidence of diabetes has remained steady, there has been a 31% increase in the prevalence of the disease between 1995 and 1999 in Ontario.[1] Management of diabetes mellitus focuses on blood glucose control and the modification of risk factors in order to prevent long-term complications such as cardiovascular, renal and retinal disease.

For patients with non-insulin dependent diabetes, the 2003 Canadian Diabetes Association (CDA) Clinical Practice Guidelines recommend diet and lifestyle modification (e.g. smoking cessation, physical activity, etc.) with the addition of oral antidiabetic agents and insulin if blood glucose control is not achieved.[2] Metformin and glyburide, alone or in combination, are considered first-line oral agents. They have been shown to effectively reduce blood glucose levels and decrease the risk of mortality.[3,4] Target hemoglobin (Hb) A_{1c} levels of ≤7.0%; fasting blood glucose levels of 4-7 mmol/L; and 2 hour post-prandial plasma glucose levels of 5-10 mmol/L are recommended for most patients. It is also recommended that a lower target HbA1c level of ≤6.0% should be considered if possible.

Control of hypertension, hypercholesterolemia and microalbuminuria are also integral to the treatment of diabetes. The CDA guidelines recommend angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension and renal disease. Aspirin therapy is also recommended for patients with diabetes with cardiovascular disease.

The following provides an overview of the Drug Quality and Therapeutics Committee (DQTC) Modernization Review of treatment for blood glucose control in diabetes; and to clarify both the outcome (i.e. recommendations) and the process by which those recommendations were made. Modernizing the Formulary is a means to ensure that the list of Formulary benefits meets current standards of safety, efficacy and cost-effectiveness in light of the most recent clinical knowledge and practice.

A comprehensive review of treatments for blood glucose control was conducted in 2003-2004 to ensure that reimbursement of diabetes medications reflects current clinical knowledge and data on efficacy, safety, and cost-effectiveness. The review consisted of a series of meetings with DQTC members and external consultants including endocrinologists, and experts in internal medicine, epidemiology, and health economics. Available clinical and economic literature and information from manufacturers were reviewed. The DQTC's recommendations for these products are described on the following pages.

The DQTC Formulary Modernization Review

Highlights of changes to Formulary coverage of treatments for blood glucose control:

- Chlorpropamide and tolbutamide will be delisted. This change will not take effect until Summer 2005 to allow transition to other treatments.
- Gliclazide (Diamicron®/MR®), repaglinide (GlucoNorm®), pioglitazone (Actos®) and rosiglitazone (Avandia®) will continue to be considered through the ICR (Section 8) mechanism.
- ICR (Section 8) requests may now be approved for up to 5 years.
- Glimepiride (Amaryl®), nateglinide (Starlix®) and rosiglitazone/metformin (Avandamet®) will not be listed on the Formulary nor reimbursed through the ICR (Section 8) mechanism.
- Revised criteria for insulin analogues insulin lispro (Humalog®), insulin aspart (NovoRapid®), and insulin lispro/insulin lispro protamine (Humalog Mix25®).

Oral Agents:

Biguanide

- **Metformin** is a first line agent for managing type 2 diabetes mellitus, particularly in overweight patients. The UKPDS 34 study showed that metformin causes less weight gain and hypoglycemia than sulfonylureas.[4] In addition, the risk of myocardial infarction was reduced by 39% in the metformin-treated group versus the conventional diet therapy group. A cost-effectiveness study of this trial showed metformin to be a cost-saving intervention.[5] Due to its proven efficacy, safety, and cost-effectiveness, **metformin** will continue to be listed as a General Benefit in the Formulary.

Insulin Secretagogues – Sulfonylureas

- **Glyburide** was shown to reduce microvascular events in the UKPDS 33 study.[3] An economic evaluation of the study found that intensive treatment including glyburide is cost-effective compared to conventional diet therapy.[6] Given its proven efficacy, safety, and cost-effectiveness, **glyburide** will continue to be listed as a General Benefit in the Formulary.
- Tolbutamide has been associated with an increased risk of cardiovascular mortality.[7] Based on the UKPDS 33 study, systolic and diastolic blood pressure (BP) were significantly higher throughout the study in patients assigned to the chlorpropamide group than any other treatment group.[3] Given the availability of effective alternatives on the Formulary, **chlorpropamide** and **tolbutamide** will no longer be listed. To allow changes to therapy, this listing change will not take effect until Summer 2005 for patients currently receiving these therapies.
- Both of the gliclazide (Diamicron® and Diamicron MR®) formulations have similar efficacy in reducing hyperglycemia, although comparisons to glyburide are inconclusive. Gliclazide is more costly than glyburide and cost-effectiveness studies do not support this additional cost. Therefore, **gliclazide** will not be listed in the Formulary, but will be considered through the ICR (Section 8) mechanism.
- There is insufficient published clinical evidence to support the efficacy of glimepiride (Amaryl®) compared to Formulary alternatives. Glimepiride is also more

Cost Comparison of Anti-Diabetic Drugs

Drug/Comparator	Average daily cost ($)	Average daily use	Average annual cost ($)	Formulary status
Biguanide				
Glucophage® and generics (metfomin)	0.24 – 0.49	1000 – 2000mg in divided doses	88 – 179	GB
Sulfonylurea				
Diabeta® and generics (glyburide)	0.04 – 0.27	2.5mg daily – 10mg bid	15 – 99	GB
Diamicron® (gliclazide)	0.38 – 1.51	80 – 160mg bid	139 – 551	NB
Diamicron MR® (gliclazide)	0.37 – 1.49	30 – 120mg daily	136 – 544	NB
Non-Sulfonylurea Secretagogue				
GlucoNorm® (repaglinide)	0.50 – 2.16	0.5 – 4mg before meals	183 - 788	NB
Alpha-glucosidase Inhibitor				
Prandase® (acarbose)	0.68 – 0.94	50 – 100mg tid	248 – 343	LU*
Thiazolidinedione				
Actos® (pioglitazone)	2.46 – 4.15	15 – 45mg daily	898 – 1515	NB
Avandia® (rosiglitazone)	1.23 – 2.76	2 – 8mg daily	449 – 1007	NB

GB – General Benefit; LU – Limited Use; NB – Not a listed benefit (May be considered through ICR/Section 8 mechanism)

*Listed as a Limited Use benefit. The reimbursement criteria are available in the current edition of the formulary. Please refer to the individual product monographs for prescribing information.

costly than other alternatives. Therefore, **glimepiride** will not be listed in the Formulary, nor considered for reimbursement through the ICR (Section 8) mechanism.

Insulin Secretagogues – Non-Sulfonylureas

- Repaglinide (GlucoNorm®) may have a role in patients with renal impairment or intolerance to sulfonylureas. There are no long-term outcomes data or cost-effectiveness data to support the listing of repaglinide. Therefore, **repaglinide** will not be listed in the Formulary, but will be considered through the Individual Clinical Review (ICR; Section 8) mechanism.
- Head-to-head comparisons of nateglinide (Starlix®) and other antidiabetic agents have not been favourable for nateglinide. Nateglinide appears to be less efficacious than glyburide in lowering fasting plasma glucose[8] and is similar in cost to other alternatives such as repaglinide. Therefore, **nateglinide** will not be listed in the Formulary, nor considered for reimbursement through the ICR (Section 8) mechanism.

Alpha-Glucosidase Inhibitor

- There was no new clinical evidence to support enhanced efficacy and cost-effectiveness with acarbose (Prandase®) compared to listed formulary alternatives. Therefore, given its higher cost versus metformin and glyburide, **acarbose** will continue to be listed as a Limited Use Benefit in the Formulary using the current criteria.

Thiazolidinediones (glitazones)

- There are no long-term data available evaluating the morbidity and mortality associated with the long-term use of the glitazones; and no head-to-head studies comparing them to glyburide, metformin or the combination of glyburide and metformin. There is significant concern regarding the lack of appropriate cost-effectiveness data available for these agents, as well. Therefore, **pioglitazone** (**Actos**®) and **rosiglitazone** (**Avandia**®) will not be listed in the Formulary, but will be considered through the ICR (Section 8) mechanism.
- The combination product of rosiglitazone and metformin, Avandamet®, was found to be restrictive for dose titration and more expensive at maximum doses than the individual agents. Therefore, **Avandamet**® will not be listed in the Formulary, nor considered through the ICR (Section 8) mechanism.

It should be noted that the products to be considered under the Individual Clinical Review (ICR; Section 8) mechanism may also be eligible for an extended approval period (of up to 5 years). In addition to long term renewals for some products, other measures, such as forms based on DQTC guidelines, are being implemented to improve response times to ICR requests.

ICR requests will be considered for the treatment of type 2 diabetes in a patient with at least one of the following:

- Inadequate glycemic control using maximal doses of glyburide and metformin
- Demonstrated intolerance or contraindication to metformin and are on maximal doses of glyburide
- Demonstrated intolerance or contraindication to glyburide and are on maximal doses of metformin
- Demonstrated intolerance or contraindication to both glyburide and metformin
- Inadequate control (greater than 50% of levels) of fasting blood glucose levels (FBG >7mmol/L) or post-prandial plasma glucose (PPG >10mmol/L) levels while using maximally tolerated doses of glyburide and metformin despite having HbA1c at target (≤ 7%).

For more information on the ICR (Section 8) submission process, see Part VIII of the Formulary. See also the request form for oral antidiabetic agents.

Insulins:

- Insulins have General Benefit listing in the Formulary, while the newer insulin analogues have Limited Use listing. There are no head-to-head comparisons of the two insulin analogues. Comparisons of the insulin analogues and human insulin have shown that the analogues may have a role in the reduction of post-prandial glucose levels. However, the insulin analogues are greater in cost and have not been shown to be cost-effective. Therefore, the insulins will continue to be listed as General Benefits and the insulin analogues will continue to be listed as Limited Use Benefits with revised criteria.

- **Insulin lispro** (**Humalog**®) and **insulin aspart** (**NovoRapid**®) will continue to be listed as Limited Use Benefits with the following revised criteria:
  - Patients with type 1 diabetes mellitus
  - Patients with type 2 diabetes mellitus using insulin in an intensive regimen (≥3 injections/day or pump)
  - Patients with type 2 diabetes mellitus with recurrent hypoglycemia, or inadequate post-prandial glucose control on a less intensive regular insulin regimen.

- **Humalog Mix25**® will continue to be listed as a Limited Use Benefit with revised criteria:
  - Insulin-requiring diabetic patients with recurrent hypoglycemia, or inadequate post-prandial glucose control on ≥2 doses mixed insulin/day.

References

1. Hux J and Tang M. Patterns of prevalence and incidence of diabetes: In Hux JE, Booth GL, Slaughter PM, Laupacis A (eds). Diabetes in Ontario: An ICES Practice Atlas: Institute for Clinical Evaluative Sciences. 2003: 1.2-1.18.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2003; 27(suppl 2).
3. 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: 837-853.
4. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65.
5. UK Prospective Diabetes Study Group. Cost effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with Type II diabetes (UKPDS No. 51). Diabetologia 2001; 44: 298-304.
6. Gray A, Raikou M, McGuire A, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomized controlled trial (UKPDS 41). BMJ 2000; 320: 1373-8.
7. University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Diabetes 1976; 25: 1129-53.
8. Hollander PA, Schwartz SL, Gatlin MR, et al. Importance of early insulin secretion: comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. Diabetes Care 2001; 24(6): 983-8.

Your feedback on this bulletin is welcomed.

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