Emerging Drug List
NATEGLINIDE

CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT

NO. 6 APRIL 2001

Generic (Trade Name): **Nateglinide** (Starlix®)

Manufacturer: Novartis Pharmaceuticals

Indication: As monotherapy, or in combination with metformin, for patients with type 2 diabetes whose blood glucose is not controlled by diet and exercise alone.

Current Regulatory Status: In the United States, nateglinide received marketing approval by the Food and Drug Administration (FDA) in December 2000. It is also approved in other countries world-wide, including Japan, Switzerland, Brazil, Mexico and Venezuela. Currently, nateglinide is under review in Canada, with a projected marketing date of mid to late 2001.

Description: Diabetes mellitus is a common chronic disease, which has been diagnosed in over 1.5 million Canadians. Treatment is aimed at improving metabolic control, thereby preventing the development, or delaying the progression, of complications associated with the disease (such as nephropathy, retinopathy, neuropathy). Nateglinide is a D-phenylalanine derivative, also classed as a meglitinide analogue. Its therapeutic effect is derived from its action on the ATP-regulated potassium channels. This is similar to sufonylureas, however, it does bind at different sites on the beta cells. It is aimed at minimizing the post-prandial rises in blood glucose, stimulating rapid, short-acting postprandial insulin secretion. In comparison to repaglinide, it is thought to be faster acting and have a shorter duration of action, thereby minimizing the risk of post-absorptive hypoglycemia. This difference will need to be borne out in comparative clinical trials. The typical dose would range from 60-120 mg three times daily, given shortly before meals.

Current Treatments: For some patients, diet and exercise alone are acceptable means for controlling blood glucose. However, for many patients, this intervention does not suffice and pharmacologics are required. There are many different classes of medications, with varied mechanisms of action, that can be used in patients with type 2 diabetes. In Canada, there are numerous products belonging to several classes. Typically, pharmacotherapy consists of sulfonylureas (i.e. tolbutamide, Diamicron®, Dia$eta®), meglitinide analogues (i.e. GlucoNorm®), biguanides (i.e. Glucophage®), alpha glucosidase inhibitors (i.e. Prandase®) and thiazolidinediones (i.e. Actos®, Avandia®).

Cost: In the U.S., a dose of 60 mg tid and 120 mg po tid are approximately $70.00-$79.99 and $80.00-$89.99/month, respectively.

Evidence: To date, clinical trials with nateglinide have included more than 3,100 type 2 diabetics. The studies have examined both monotherapy and combination therapy with nateglinide.

Horton *et al* conducted a 24-week trial assessing the efficacy and tolerability of nateglinide and metformin alone or in combination in type 2 diabetics. At enrollment, patients had a glycated hemoglobin of 6.8 to 11.0 %. Patients were randomized in a double-blind fashion to receive nateglinide 120 mg before meals (n=179), metformin 500 mg three times daily (n=178), a combination of both medications (n=172) , or placebo (n=172). At the end of the study, fasting plasma glucose levels were improved in the treatment groups; changes were -0.7, -1.6, -2.4 and +0.4 mmol/L for the nateglinide, metformin, combination and placebo groups, respectively ($P \leq 0.0001$ versus placebo, $p \leq 0.01$ versus monotherapy). For glycated hemoglobin, a similar trend

Evidence (con't): was noted [-0.5, -0.8, -1.4, +0.5% ($P \leq 0.0001$ versus placebo, $p \leq 0.01$ versus monotherapy)]. Both nateglinide or combination therapy showed a greater reduction in glucose levels after challenge with Sustacal.

Adverse Effects: Adverse effects that were reported included gastrointestinal distress and symptoms suggestive of hypoglycemia (e.g. increased sweating, dizziness, tremor, increased appetite). Typically, the hypoglycemia has been mild in nature. To date, clinically significant changes in liver function tests during nateglinide therapy have not been described.

Conclusion: Diabetes mellitus, a problem involving insulin resistance and abnormal beta cell function, results in fluctuations in blood glucose levels outside of normal ranges. Without intervention to control blood sugars, this can lead to both microvascular and macrovascular complications. The disease itself, and its complications, can be very costly to the health care system. New avenues for the treatment of this condition are welcome in curbing the debilitating impact of diabetes. The clinical trials available do suggest that nateglinide is an efficacious and well-tolerated agent for the treatment of type 2 diabetes. Its pharmacodynamic profile may be more favorable in contrast to currently available medications. Its true role in the treatment algorithm, along with its advantage/disadvantage profile, will have to be discerned through well-designed comparative trials and clinical practice.

References:

1. Chehade JM, Mooradian AD. A rational approach to drug therapy of type 2 diabetes mellitus. Drugs 2000;60(1):95-113.
2. Clinical Pharmacology 2000. Gold Standard Multimedia. Internet site: www.gsm.com. Accessed April 20, 2001.
3. Dunn CJ, Faulds D. Nateglinide. Drugs 2000;60(3):607-15.
4. Doctor's Guide to the Internet. FDA approves Starlix (nateglinide) for type 2 diabetes. Internet address: www.pslgroup.com/dg/1EE36E.htm. Accessed January 2, 2001.
5. Medical Industry Today. Starlix expands type II diabetes drug options. Internet site: www.medicaldata.com/members/mit/detail.asp?art+12260004&MITUID=205840. Accessed January 2, 2001.
6. Meltzer S, Leiter L, Daneman D, et al. 1998 clinical practice guidelines for the management of diabetes in Canada. Can Med Assoc J 1998;159 (8 Suppl):S1-29.

The contents of this bulletin are current as of April 2001.
The Emerging Drug List highlights drugs not yet approved in Canada that are anticipated to have a significant impact on the health care system. Minimal information is available about these drugs, and they may in future become the subject of an early assessment.

ISSN # 1496-8398