

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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## Exenatide

After ingestion of a meal, intestinally-derived signals called incretins stimulate insulin secretion. As this effect is impaired in patients with type 2 diabetes mellitus, the incretin signalling pathway presents an attractive target for a number of novel glucoregulatory compounds. Further information about incretins was recently published in another RGH E-Bulletin, refer to volume 31(7).

Exenatide (Byetta<sup>®</sup>) is the first compound in a new class of antihyperglycaemics - the incretin mimetics. It is a synthetic peptide with properties similar to glucagon-like peptide-1 (GLP-1), an incretin hormone that regulates energy homeostasis. Unlike naturally occurring GLP-1, exenatide is resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4).

Exenatide improves glycaemic control by a number of mechanisms. Insulin secretion is mediated through binding to GLP-1 receptors in pancreatic  $\beta$  cells. This occurs in a glucose-dependant manner, with insulin being released during hyperglycaemia but not hypoglycaemia or euglycaemia. Similarly, plasma glucagon levels are suppressed in hyperglycaemic patients. In addition, exenatide slows gastric emptying, which reduces the rate of glucose absorption after a meal. Other possible mechanisms include stimulation of pancreatic  $\beta$  cell neogenesis and proliferation.

Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are suboptimally controlled with metformin and/or a sulfonylurea. To achieve adequate glycaemic control, twice daily subcutaneous injections of 5 or 10 $\mu$ g exenatide are required. At present the supply of exenatide is not subsidised under the auspices of the Australian Pharmaceutical Benefits Scheme (PBS)>

The most common adverse events associated with exenatide are gastrointestinal, including nausea, vomiting and diarrhoea. Nausea occurs more frequently at the start of treatment and gradual dose escalation has been found to attenuate this side effect. The incidence of hypoglycaemia is low and is more common when exenatide is used in combination with a sulfonylurea. Acute pancreatitis has also been reported in postmarketing surveillance with exenatide.

Exenatide has no adverse effects on weight, and is rather associated with significant and progressive weight loss, which in itself has the potential to improve glycaemic control.

Due to delayed gastric emptying, there is a potential pharmacokinetic interaction with concomitantly administered oral drugs. Patients who are taking medication that rely on threshold concentrations for efficacy (eg contraceptive pill or antibacterials) should be advised to take these at least one hour before exenatide administration.

Currently, a long acting release (LAR) formulation of exenatide is being investigated in phase III trials. Exenatide LAR uses biodegradable polymeric microspheres to entrap exenatide, which over time release the molecule in a controlled manner. The formulation is designed for once weekly subcutaneous administration. Exenatide LAR can potentially improve glycaemic control by providing 24 hour exposure to therapeutic drug concentrations, as well as having the added convenience of a once weekly injection regimen.

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