THE NORTHERN HOSPITAL

# EXENATIDE

*"Blue Dancers" pastel on paper, c. 1899, Edgar Degas, Pushkin Museum, Moscow.*

**Paul:** *Mon dieu, where the devil is he? The performance is about to begin!*

**Ludovic:** *Hush, Paul, you know very well where he is, he'll be here shortly, he never misses the rise of the curtain!*

**Paul:** *My god Ludovic, please tell me he hasn't brought his infernal sketchbooks with him again!"*

**Ludovic:** *Of course he has Paul - he's down in the Foyer de la Danse right now - I've never seen him so concentrated!*

**Henri:** *I have! When we were on guard duty one night during the war. We thought we heard Prussians!...He would not have shot them of course, but sketched them I have no doubt of it! You would agree with me my brother?*

**Alexis:** *Ha, ha, yes, he probably would have. Shhh! Here he comes!*

**Paul:** *Edgar, you are late again what the devil have been doing? This loge has cost me a fortune! You don't understand the difficulties I went to, to obtain these seats! You could at least be punctual. Why didn't you come with us in my carriage?*

**Edgar:** *Now Paul you know I do not like carriages. One sees no one. That is why I love the omnibus. One can observe the people. We were created to observe one another.*

**Ludovic**: *Well observe down there everyone, there she is!! Mon dieu I do declare I was created to see her! I shall be arranging for an introduction!*

**Henri:** *Who is she?*

**Ludovic:** *You uncultured imbecile Henri, I don't understand why I invite you to the Opera. That's Eugénie Fiocre, the darling of all Paris!*

**Edgar:** *Where? Where? Which one is she?*

**Ludovic:** *In the center there Edgar. The one adjusting her straps.*

**Edgar:** *That one?*

**Ludovic:**. *No, the one behind her, do be quiet now, the curtain is about to go up!*

**Edgar:** *Yes, yes I see her now !!*

*Suddenly hundreds of gas lamps light up as one, flooding the stage with brilliant light. The audience is ecstatic. Thunderous applause. The orchestra bursts into life. The dancers seem to glow eerily, an iridescent blue. They are electrified, the adrenaline runs as frantic last second adjustments are made. This is the fleeting instant, that Edgar has*

*been waiting for. His photographic memory records the scene below him. The curtain goes up and in an instant the dancers have leapt out onto the stage; but the image of them in the wings stays within Edgar's mind, and he will bring it back to his studio and complete a pastel, or a series of pastels at leisure, perhaps tomorrow or the next day or perhaps, even many years later. He continues to sketch in frenzied short sharp, precise lines.*

**Henri:** *Are you going to make one of those Impressionist paintings, Edgar?*

**Edgar:** *Henri, no! I have told you before. I am not an "Impressionist". I am a Realist, I simply use their modern style.*

**Henri:** *But you are so…..so…..spontaneous!*

**Edgar:** *Henri, no art is less spontaneous than mine. What I do is a result of reflection and studies of the old masters. Of inspiration, spontaneity, temperament I know nothing.*

**Henri:** *I do not understand you at all Edgar. But now, where are you going? The performance has only just begun!*

**Edgar:** *I've seen all I need to see. I'm going back to the Foyer now. I must have the right position for when they return there at the end of this first act.*

*Henri is nonplused, he casts a questioning look toward Ludovic.*

**Ludovic:** *Leave him be Henri, he is only interested in the lines, the movement, the light, the colour, the moment. If I did not know him better I would say he was…..an Impressionist!*

*Edgar's motives for engaging with his dear friends in the prestigious loges are not quite as direct as they had imagined! His friends are merely a means to his true end!*

*And so it is with the new glucagon-like peptide-1 analogues! They engage their dear friends the incretins, and by their agency they may achieve their own true ends!*

# EXENATIDE


*Pre-filled autoinjector, 10 micrograms, exenatide.*

## Introduction

**Exenatide** is a novel **injectable** antidiabetic agent, used in the treatment of **type II diabetes mellitus.**

It is **not** an insulin

It is a **glucagon-like peptide-1** (**GLP -1**) **analogue** that acts by:

1. Increasing insulin secretion.
2. Reducing glucagon secretion.
3. Causing a small reduction in appetite.
4. Slowing gastric emptying.

Exenatide is recommended as an adjunct in patients with type 2 diabetes mellitus with:

1. Metformin and/or a sulfonylurea, when these are inadequate.

2. Metformin and a basal insulin, when these are inadequate.

Two formulations are available in Australia:

1. **"Byetta"** (trade name) - a twice daily SC dosing agent for close control.

2. "**Bydureon**" (trade name) - a long acting depot **once weekly** SC dosing agent.

## History

Exenatide is a synthetic version of **exendin-4,** a hormone found in the saliva of the **Gila monster lizard.**

Exendin-4 was first isolated by endocrinologist, **Dr. John Eng**, in 1992 while working at the Veterans Administration Medical Center, New York.

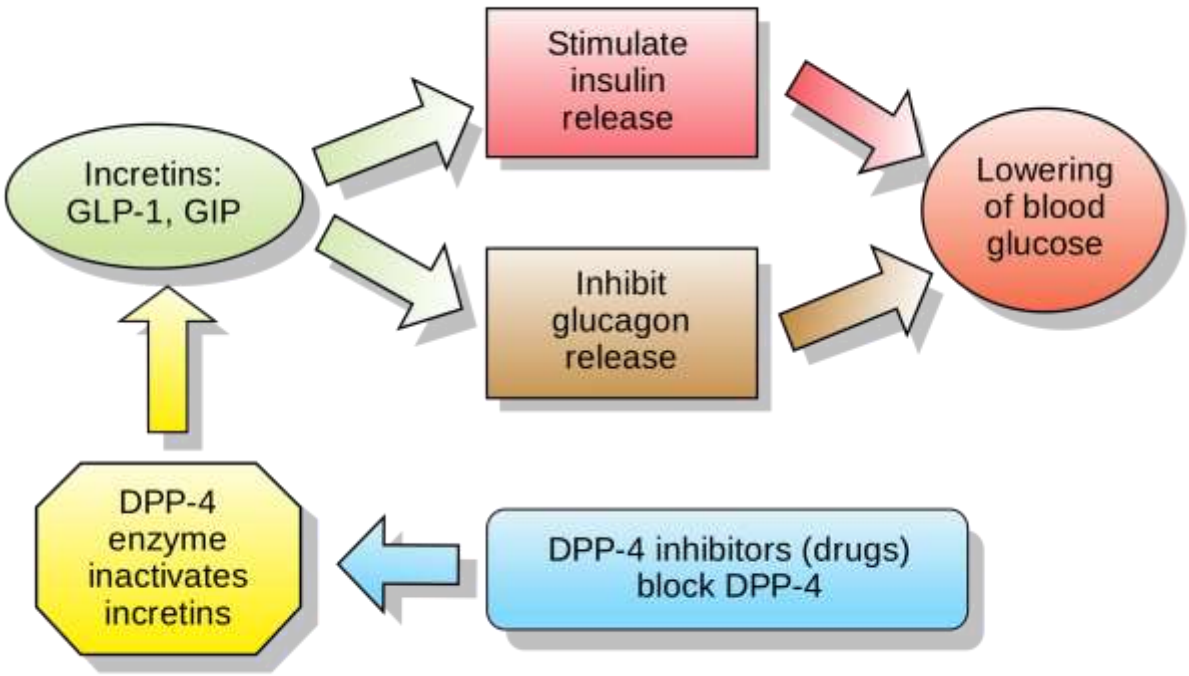
It binds to the intact human Glucagon-like peptide-1 receptor (GLP-1R) in a similar way to the human peptide glucagon-like peptide-1 (GLP-1) and produces similar actions.

## Chemistry

Exenatide is a **synthetic** 39 amino acid **peptide amide.**

The amino acid sequence of exenatide partially overlaps that of natural human GLP-1.

## Physiology



**Incretins** are a group of hormones that:

- Stimulate insulin release
- Inhibit glucagon release

The two principal **incretin** hormones are:

1. Glucose - dependent insulinotropic polypeptide (**GIP**) - (*formerly and less correctly known as Gastric inhibitory polypeptide*).
    - It is synthesized by K cells, which are found in the mucosa of the duodenum and the jejunum of the gastrointestinal tract.
    - It stimulates the production of insulin from the beta cells of the pancreas.
2. Glucagon-like peptide - 1 (**GLP -1**):
    - It is synthesized by L cells which are primarily found in the ileum and large intestine.
    - It stimulates the production of insulin from the beta cells of the pancreas in response to rising glucose, while also suppressing glucagon secretion from the alpha cells of the pancreas.

The incretin hormones are part of an endogenous system involved in the physiological regulation of glucose homeostasis.

Incretin hormones are released by the **intestinal tract** in response to an oral **glucose load.**

Type 2 diabetics are less responsive to GIP and have lower levels of GIP secretion after a meal when compared to non-diabetics.

## Classification

There are currently 6 classes (6 oral and one injectable within the Incretin-based therapies) of non-insulin hypoglycemic agents available in Australia:

*The two principle classes are:*

1. **The Biguanides**:

    *These agents act by reducing hepatic glucose production (i.e. gluconeogenesis) and increasing the peripheral utilization of glucose.*

    *Examples include:*

- Metformin

2. **The Sulphonylureas**:

*These agents act by increasing pancreatic insulin secretion and also possibly by enhancing peripheral sensitivity to insulin:*

*Examples include:*

First generation:

- Tolbutamide (no longer used)

Second generation, (more potent, lower doses):

- Glibenclamide
- Gliclazide
- Glipizide

Third generation:

- Glimepiride

*Other newer agents with less clinical experience include:*

3. **Incretin-based therapies**:

Dipeptidyl peptidase - 4 inhibitors (i.e. **DPP - 4 inhibitors** or "**Gliptins**"):

*These agents increase the concentrations of incretin hormones (GLP-1 and GIP) that are produced in the gut following ingestion of food; GLP-1 stimulates insulin release, and reduces glucagon secretion.*

*Examples include:*

- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin
- Vildagliptin

Glucagon-like peptide-1 (GLP-1) receptor agonists:

*These agents are synthetic analogues of GLP-1; they increase insulin secretion and reduce glucagon secretion and also cause a small reduction in appetite.*

*Examples include:*

- **Exenatide**
- Liraglutide
- Dulaglutide

4. **Glucosidase inhibitors**:

*These agents reduce the breakdown of complex carbohydrate in the gut, thereby reducing absorption of carbohydrate and hence insulin requirements*

*Examples include:*

- Acarbose.

5. **Thiazolidinediones (or "Glitazones")**:

*These agents reduce peripheral insulin resistance and hence insulin requirements*

*Examples include:*

- Pioglitazone
- Rosiglitazone

6. **Sodium-glucose co-transporter 2 (or SGLT-2) inhibitors (or "Gliflozins")**:

*These agents reduce glucose reabsorption in the kidneys.*

*Examples include:*

- Dapagliflozin
- Empagliflozin
- Ertugliflozin

## Preparations

Exenatide as:

Solution: Prefilled injectors:

- 5 mcg/dose (60 doses), (trade name "**Byetta"**)
- 10 mcg/dose, (60 doses), (trade name "**Byetta"**)

Pre-filled pen with powder (containing extended release microspheres) and solvent:

- 2 mg (powder + solvent) (trade name "**Bydureon"**)

## Mechanism of Action

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that acts by:

1. Increasing insulin secretion
2. Reducing glucagon secretion
3. Causing a small reduction in appetite.
4. Slowing gastric emptying.

## Pharmacodynamics

Exenatide improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

Modest weight loss (2-3 kg) has been observed, but *long term* effect on weight is currently unknown.

**Once-weekly** exenatide appears to be more effective in **reducing HbA1c** over 30 weeks than twice-daily exenatide.

## Pharmacokinetics

### *Absorption:*

- Exenatide is administered by subcutaneous injection.

  Median peak plasma concentrations are reached in approximately 2 hours.

  Exenatide is *not* recommended to be administered by intravenous or intramuscular injection

### *Distribution*

- The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide is 28.3 L.

- Degree of protein binding is unknown.
- It is unknown if exenatide crosses the human placenta.
- It is unknown if exenatide is distributed into human breast milk.

*Metabolism and excretion:*

- Exenatide is predominantly eliminated by **glomerular filtration** with subsequent proteolytic degradation.
- As exenatide is cleared primarily by the kidney; hepatic dysfunction is not expected to affect blood concentrations of exenatide.
- Half - life is 2.4 hours.

Note that effects of the **long (weekly) acting formulation** may continue after stopping treatment, as plasma concentrations decline over about **10 weeks**. It is important to consider this with regard to adverse effects and when choosing subsequent treatments.

## Indications

Exenatide is recommended as adjunctive therapy in patients with **type 2 diabetes mellitus** with:

1. Metformin and/or a sulfonylurea, when these are inadequate.
2. Metformin and a basal insulin, when these are inadequate.

Exenatide is **not** a substitute for insulin in insulin requiring patients.

Exenatide should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

## Contra-indications/precautions

These include:

1. Known hypersensitivity to exenatide
2. Renal impairment:
    - Contraindicated if CrCl < 30 mL/minute.

      Elimination may be reduced possibly increasing the risk of adverse effects.

3. Severe GIT disease:

    - e.g. gastroparesis, dumping syndrome: avoid use due to effects on the GIT.

4. History of pancreatitis (contraindicated).

5. Gall bladder disease:

    - GLP-1 analogues *may* increase the risk of gall bladder disease and the need for cholecystectomy.

*Pregnancy*

Exenatide is classified as a category C drug with respect to pregnancy.

Category C class drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Published reports describing the use of exenatide in human pregnancy have not been located.

Due to potential adverse effects, dietary modification and insulins should be considered as alternative therapies to exenatide during pregnancy.

Follow-up and monitoring of both maternal and fetal wellbeing by a multidisciplinary team is recommended to ensure optimal glycaemic control and fetal growth.

*Breast feeding*

Published reports describing the use of exenatide during breastfeeding have not been located.

The transfer of exenatide into the breast milk is limited by the high molecular weight of the medicine.

However, due to potential adverse effects in the breastfed infant, consider an alternative treatment while undergoing exenatide therapy.

## Adverse Effects

These include:

1. Hypersensitivity or allergic reactions:

    - Including anaphylaxis

- Injection site reactions:

    - ♥ Injection site reactions have been reported in approximately 5 % of subjects receiving exenatide in long-term (26 weeks or longer) controlled clinical trials.

      These reactions have usually been *mild* and usually did not result in discontinuation of exenatide.

2. GIT upset:

    - GIT upset is **common** and may include, nausea and/or vomiting diarrhoea, constipation, dyspepsia

    - Symptoms usually improve however with continued treatment.

3. Hypoglycaemia:

    - Hypoglycaemia is *unlikely* unless GLP−1 analogue is used with a **sulfonylurea** or **insulin**

4. Antibodies:

    - **Anti-exenatide antibodies** may develop in up to **50% of patients** and are more common with the once-weekly dose than with the twice-daily dose.

      Although early trial data suggest that these are clinically unimportant, those who develop higher titers *may* have a diminished glycaemic response (3% of patients in controlled trials) and a higher rate of injection site reactions.

5. Cholelithiasis / cholecystitis

6. Renal impairment.

7. Pancreatic complications:

    - This is an area of uncertainty. There is some concern over subclinical pancreatitis and more importantly pancreatic cancer

      GLP-1 analogues have been implicated with pancreatic adverse effects: however most studies suggest the risk of acute pancreatitis is likely to be very low, (data collection is ongoing).

8. Injection site reactions:

- Injection site reactions occur more frequently with the **once-weekly** dosing regimen than with the twice-daily dosing regimen.

## Dosing

Byetta, (twice daily):

Usual dosing for exenatide in adults is:

- Exenatide SC injection initially **5 micrograms twice daily**, within 60 minutes before morning and evening meals (or before 2 main meals at least 6 hours apart).

- If initial dose is tolerated, after 1 month increase to **10 micrograms twice daily.**

  **The aim of initial dose titration is to improve GI tolerability**

Bydureon, (once weekly):

**Bydureon** is a long acting preparation that can be given **2 mg** subcutaneously **once a week.**

Inject once a week on the same day each week, with or without a meal.

Carefully follow instructions for mixing the powder with the liquid in the pen; **inject immediately after mixing**.

Note that effects of the long acting formulation may continue after stopping treatment, as plasma concentrations decline over about **10 weeks**. It is important to consider this with regard to adverse effects and when choosing subsequent treatments.

*Monitoring:*

Less frequent blood glucose concentration monitoring is required with a GLP−1 analogue than with insulin

*Exposition du Palais Garnier (Christian Leiber)*

*References*


1. eTG - October 2019

2. Exenatide in Australian Medicines Handbook Website, July 2019.

3. Exenatide in MIMs Website:

    - Byetta Solution, 1 June 2017.

    - Bydureon powder, 1 April 2019.

4. Exenatide in RWH Pregnancy and Breast feeding Guidelines, 15 January 2019.



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