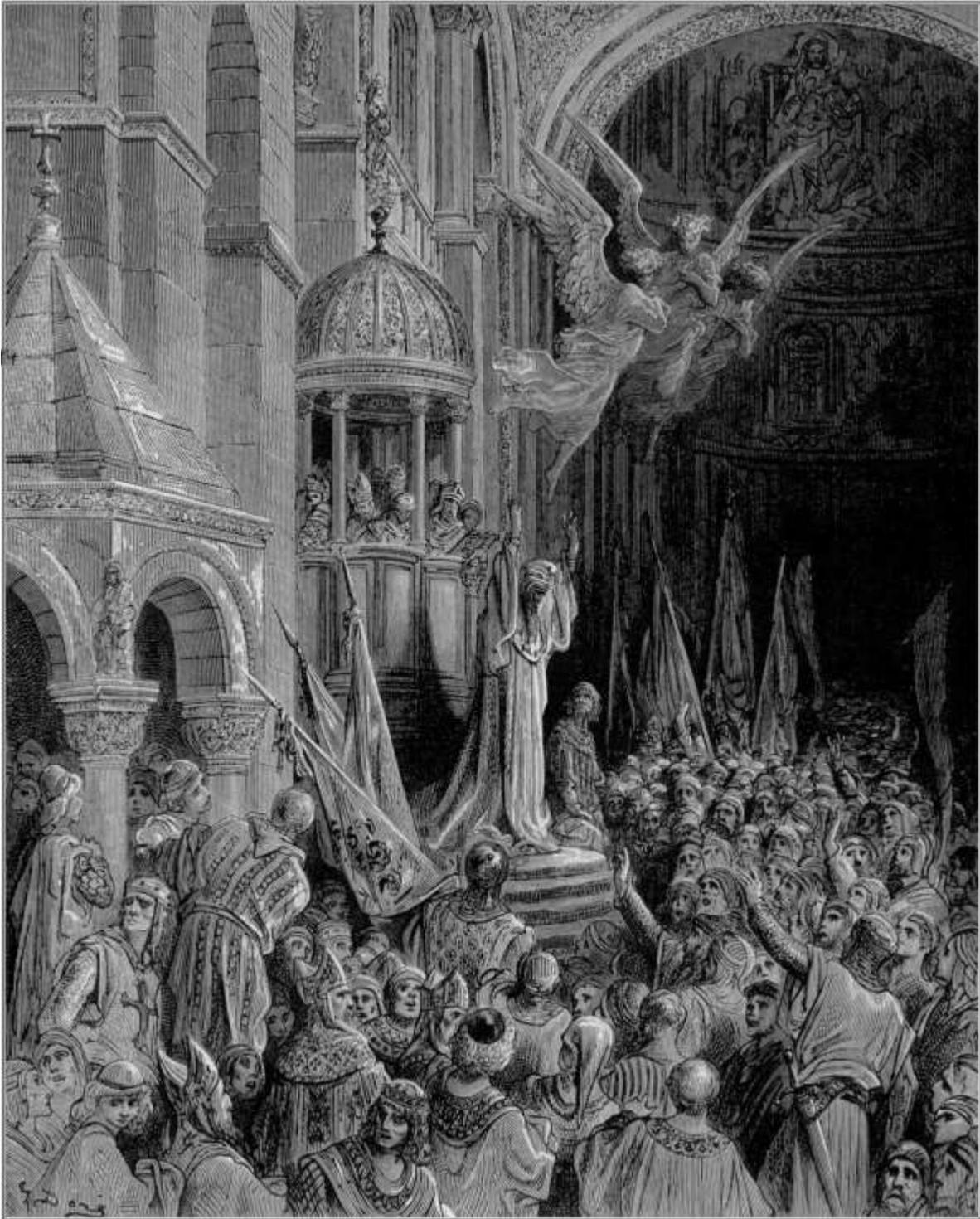


**ROSIGLITAZONE**



*The Doge of Venice, Enrico Dandolo, preaching the Fourth Crusade in the Cathedral of St. Mark, Lent, 1201, woodcut print, 19th century, Gustave Dore.*

*“...he assembled at least ten thousand men in the church of St Mark, the most beautiful that there is, to hear Mass and to pray to God for guidance. And after the Mass he summoned the envoys and besought them, that they themselves should ask of the people the services they required. Geoffrey de Villehardouin, Marshal of Champagne, spoke by consent for the others....Then the Doge and people raised their hands and cried aloud with a single voice, “We grant it! We grant it!” And so great was the noise and tumult, that the very earth seemed to tremble underfoot...*

*(And the Doge replied), “Signors, you are joined with the worthiest people in the world, for the highest enterprise ever undertaken. I myself am old and feeble; I need rest, my body is infirm. But I know that no man can lead you as I, your Lord, can do. If therefore you will allow me to direct and defend you by taking the Cross, while my son remains in my place to guard the Republic, I am ready to live and die with you and the pilgrims”.*

*And when they heard him, they cried with one voice, “We pray God that you will do this thing, and come with us!”....so he came down from the pulpit and moved up to the altar, and knelt there, weeping; and he had the cross sewn onto his great cotton hat, so determined was he that all men could see it....*

*Geoffrey de Villehardouin, Lent, 1201.*

*The kindest thing that can be said about the Third Crusade, the magisterial John Julius Norwich wrote, was that it was a “distinct improvement on the Second”. Although Acre, Jaffa and other towns were reclaimed for Christendom, the major prize, that of Jerusalem, had eluded Richard Coeur de Lion and Philip Augustus of France. The Third Crusade had achieved much, but the main prize was still to be had. In 1198, Pope Innocent III, on being elected the next successor of St. Peter, had immediately called for a Fourth Crusade, to recover the Holy City. By doing so, however, Norwich explains, Innocent unwittingly, brought about the greatest triumph in the thousand year history of the Venetian Republic. The “grim adventure”, still “ludicrously known as the “Fourth Crusade”, and its architect, Venice’s greatest Doge, Enrico Dandolo, would prove to be the darkest and most shameful episode in Christendom”.*

*It is unknown exactly how old Enrico Dandolo was when he was elected Doge of Venice on 1st January, 1193. It was said that he was eighty five and already stone blind. Though this hardly seems credible, he was nonetheless certainly an old man, more probably in his mid seventies. King Richard had declared that if the Muslim east was to be attacked again, Egypt, as the weakest point, was where this attack should be. This meant a seaborne invasion, and there was only one fleet in existence which could transport such a large army - the Venetian fleet. The French leader of the Crusade, the Marquis Boniface - Tibald of Champagne, approached the Venetians in Lent of 1201, requesting their support. Unbeknown to Boniface, the Venetians had only just negotiated a lucrative trade agreement with the Sultan’s Viceroy in Cairo. They would be lukewarm on the idea of an attack on Egypt. Nonetheless, Dandolo knew a profit when he saw one. In return for half of all territories captured and the staggering sum of 84,000 ducats, Venice would supply 50 fully equipped galleys and other ships to transport the entire Crusader force to Egypt. Boniface agreed. Dandolo then called his people to St Marks, to announce the great adventure. The French chronicler Geoffrey de Villehardouin, has left a dramatic account*

*of his charismatic preaching which in quick time had the congregation of St Marks thunderously granting approval for the Crusade. It was decreed that Crusaders from across Europe would gather in Venice on St John's day, 24th June 1202, when the fleet would be ready for them.*

*Behind closed door however, the true destination, Egypt was kept a secret from the rank and file, who fully expected a landing in the Holy Land. It is uncertain if news of the true destination was leaked out by Dandolo, but one way or another, it was leaked out. Many on hearing this were outraged and either made plans for their own transport directly to the Holy Land or dropped out of the enterprise altogether. On the appointed rendezvous day, the situation was embarrassing in the extreme. Venice had kept her part of the bargain, with a magnificent fleet at the ready - but only about one third of the Crusader army turned up at the Lido. This meant that there would be no way they could pay the Venetians. Again Dandolo saw an opportunity for Venice. If the army would agree to attack the city of Zara, which Venice had recently lost to the King of Hungary and had been unable to recapture, then payment of the balance owed could be postponed. Boniface reluctantly agreed. Pope Innocent on hearing of this deal, angrily forbade it, but Boniface having little choice had already agreed. Thus it came about that on 8th November 1202, the army of the Fourth Crusade set out with 480 ships, including 50 galleys, led by the galley of the Doge himself, "painted vermilion with a silken vermilion awning spread above cymbals clashing and trumpets sounding from the bows", not for Palestine or even for Egypt, but for Zara in the Kingdom of Hungary! The Crusader army easily took Zara and then promptly put it to the sack. Almost immediately bitter arguing then broke out between the Franks and Venetians over the spoils. Pope Innocent, outraged by these proceedings, responded by excommunicating the entire expeditionary force, though later he reconsidered and restricted his ban to the treacherous Venetians only. Though the rank and file were extremely distressed, Dandolo didn't appear to mind in the least, he had Zara and its riches in Venetian hands once more. The Crusade could not be said to have got off to a good start.*

*If the Venetians were considered supremely duplicitous by Innocent, then they were total amateurs in comparison to the Byzantines. What happened next was one of the greatest examples of Greek labyrinthine intrigue that history records. A message arrived in Zara from a certain Alexius, the son of the Byzantine Emperor, Isaac II Angelus. It was an unprecedented offer of Byzantine assistance for the floundering Crusade. Both Boniface and Dandolo were astonished - Byzantium had never contributed anything to any crusade, there had to be a catch....and there was. Isaac had been deposed by his brother (another) Alexius who had usurped the throne. Young Alexius proposed that if the Crusaders would come to Constantinople and forcibly remove his evil uncle and place himself on the throne instead then he would provide three things in return. He would fully finance the Egyptian expedition, he would provide an additional 10,000 troops for the cause and, most astonishingly of all, he would re-submit the Eastern Orthodox Church back to the authority of Rome, thus healing the great schism, between Western and Eastern Christendom. The deal seemed too good to be true. Boniface discussed it with Dandolo, who accepted it with enthusiasm, probably relieved also at the chance to further distract from an invasion of Egypt. Even Pope Innocent would surely agree to this proposal. On 24th June, a year after the rendezvous in Venice, the Crusader army, with young Prince Alexius in the Doge's galley, set out from Zara, bound for Constantinople. The average*

*Frank knew virtually nothing of the fabled city of Constantine, though all had grown up on stories of its immense wealth and impregnable walls. To any medieval soldier, whether or not they bore the Cross, a fabulously wealthy city meant one thing only - loot. Geoffrey de Villehardouin left a famous account of the approach of the Crusader army to the legendary city...*

*“You may imagine how they gazed, all those who had never before seen Constantinople. For when they saw those high ramparts and the strong towers with which it was completely encircled, and the splendid palaces and soaring churches - so many, but for the evidence of their own eyes they would never have believed it - and the length and breadth of that city which of all others is sovereign, they never thought that there could be so rich and powerful a place in all the world. And mark you that there was not a man so bold that he did not tremble at the sight; nor was this any wonder, for never since the creation of the world was there so great an enterprise...”*

*Although Alexius III had had plenty of time to prepare, he had no strong fleet with which to repel the Crusaders, after his idiotic brother Isaac II had let it go to ruin through total neglect. Although the Venetian assault craft delivered soldiers with ladders to the ramparts where the hottest of fighting was taking place, the commanders were reluctant to make a beach landing, so fierce was Byzantine resistance. At this point Geoffrey de Villehardouin records probably Enrico Dandolo's and indeed Venice's finest hour. The old blind man stood on the bow of his galley and personally led it onto the beach. Ashamed at their hesitance, the rest of the fleet followed immediately on seeing the banner of St Mark planted in the sand.*

*“And there was an extraordinary feat of boldness. For the Duke of Venice, who as an old man and stone blind, stood fully armed on the prow of his galley, with the banner of St. Mark before him, and cried out to his men to drive the ship ashore if they valued their skins. And so they did, and ran the galley ashore, and he and they leapt down and planted the banner before him in the ground. And when the other Venetians saw the standard of St. Mark and the Doge's galley beached before their own, they were ashamed, and followed him ashore...”*

*As tower after tower fell into Venetian hands it was clear that Constantinople, was not going to be able to resist the entry of the Crusader army into the city. For the first time in its history the great walls of Constantine had been breached. At this point Alexius III fled the city, with 10,000 pounds of gold, leaving his wife and children, apart from a favourite daughter, behind. At this gravest crisis in its history, a hastily convened council of state came up with a brilliant plan. They retrieved old Isaac Angelus from prison and placed him back onto the Imperial throne, thus removing the moral basis for the Crusader attack. He was now even blinder than Enrico Dandolo, as his brother had taken the precaution of putting out his eyes when he deposed him. He was nonetheless, the legitimate Emperor, and now that the usurper had fled there was no longer any reason for the Crusaders to be in the city. However there remained the issue of young Alexius' promises. Boniface and Dandolo had kept their part of the bargain; Alexius had become co-emperor, (as Alexius IV), with his father Isaac on 1st August 1203. When the Greek ruling council discovered the terms which Alexius had promised the Crusaders, they were astonished. It need hardly be said that the Patriarch was outraged at having to give*

*allegiance of the Church back to Rome. Worse still the treasury appeared to be virtually empty, due to the theft and extravagances of Alexius III. Further, the Byzantine army commanders were none too keen in joining the Crusade to the Holy Land or to Egypt, as they saw little profit in it, let alone being beholden to barbarians from the west, who had created havoc, destruction and immense fires in their city. Young Alexius began to sorely regret the rash promises he had made in Zara. He decided to heavily tax his people to pay for them. This did not go down well with the people, who know only too well where the money was going to go. Greeks began to clash with the hated Crusaders throughout the city - they wanted to be rid of the uncultured thugs who were bleeding their city white. It seemed like all our war was imminent. It was now that Christendom's most shameful episode developed. Dandolo could have defused the explosive situation by simply ordering the fleet to sail away, and cutting his losses, however by now he had a new plan in mind. He had lost interest in the Crusade, especially an attack on Egypt, which would damage Venetian commercial interests. He had a much greater vision - no less that the taking of the Byzantine Empire itself. With the Crusader army inside the city, there would never be a better opportunity. As nothing more could be expected from Alexius, the throne of Byzantium would be forcibly taken from him, and the Empire would be dismembered, its territories divided up between the Venetians and various Frankish Lords. Dandolo went to Boniface saying that Alexius had betrayed them and that the only way now to pay for the expedition was the taking of the Byzantine empire. Boniface agreed. To make matters even worse, yet another Alexius - Alexius Ducas (nicknamed Murzuphlus, on account of his magnificent eyebrows), descended from a very noble family (which had already produced two Emperors) seized Alexius III and Isaac, had them imprisoned, and declared himself the new Emperor, and one who had no obligation whatsoever to fulfil the promises to his predecessors.*

*This provoked an explosive reaction from the Crusaders. On 9th April an all out attack began on the city. The Venetian fleet out in the harbour attacked again and troops poured into the city, hell bent on destruction and loot. Once the walls were breached the carnage was terrible to behold - even Geoffrey de Villehardouin was appalled at what followed. "Not since the barbarian invasions seven centuries before, had Europe witnessed such a orgy of brutality and vandalism", Norwich writes, "never in history has so much beauty, so much superb craftsmanship, been wantonly destroyed in so short a space of time. Among the witnesses, helpless, horrified, almost unable to believe that human beings who called themselves Christians could be capable of such enormities - was Nicetas Choniates:*

*"I know not how to put any order into my account, how to begin, continue or end. They smashed the holy images, hurled sacred relics of the Martyrs into places I am ashamed to mention, scattering everywhere the body and blood of the Saviour. These heralds of Anti-Christ seized the chalices and the patens, tore out the jewels and used them as drinking cups...As for their profanation of the Great Church of St Sophia, it cannot be thought of without horror. They destroyed the high altar, a work of art admired by the entire world, and shared out the pieces among themselves...and they brought horses and mules in the Church, the better to carry off the holy vessels and the engraved silver and gold that they had torn from the throne, and the pulpit, and the doors, and the furniture wherever it was to be found; and when some of these beasts slipped and fell, they ran them through with their swords, fouling the Church with their blood and ordure.*

*A common harlot was enthroned in the Patriarch's chair, to hurl insults at Jesus Christ, and she sang bawdy songs, and danced immodestly in the holy place....nor was there modesty shown to virtuous matrons, innocent maids or even virgins consecrated to God....In the streets houses, and churches could be heard only cries and lamentations...And these men carried the Cross on their shoulders, the Cross on which they had sworn to pass through Christian lands without bloodshed, to take only arms against the heathen, and to abstain from the pleasures of the flesh until their holy task was done.....*

*Constantinople fell to the army of the Fourth Crusade. The Doge placed a malleable puppet on the throne, Count Baldwin of Flanders, the first non-Greek "Emperor" in Constantinople. He was the third Emperor to be crowned in less than a year. Alexius V fled, but was later captured and horribly executed. Although the Greeks recaptured Constantinople in 1261, the city was by now was only the barest shadow of its former self, with most of its former territories irrevocably lost.*

*John Julius Norwich gives summary of the whole shameful affair:*

*"Although the Latin rule along the Bosphorus lasted less than sixty years, after which the Greek Empire was to struggle on for nearly two more centuries, that Empire never recovered its strength or any considerable part of its lost dominion. Under firm and forceful leadership - which was not lacking in the century to come - a strong and prosperous Byzantium might have halted the Turkish advance while there was still time. Instead, it was left economically crippled, territorially truncated, powerless to defend itself against the Ottoman tide. There are few greater ironies in history than the fact that the fate of Eastern Christendom should have been sealed - and half Europe condemned to some five hundred years of Muslim rule - by men who fought under the banner of the Cross. Those men were transported, inspired, encouraged and ultimately led by Enrico Dandolo in the name of the Venetian Republic; and just as Venice derived the major advantage from the tragedy, so she, and her magnificent old Doge must accept the major responsibility for the havoc they wrought upon the world".*

*The oral anti-diabetic agent rosiglitazone is one of the class of drugs known as the "glitazones". Concerns however have been raised over its safety due to a claimed association of increased risk of adverse cardiovascular events. In the great Crusade against diabetes, we need choose our allies carefully, we are mindful therefore of the old adage "With friends like that, who needs allies? As Pope innocent III discovered on establishing his mighty enterprise, that history now ludicrously knows as the "Fourth Crusade", some "allies" are simply not worth the trouble!*

## ROSIGLITAZONE

### Introduction

**Rosiglitazone** is a **thiazolidinedione** (or “**Glitazone**”) class, oral antidiabetic agent that acts primarily by **decreasing insulin resistance**.

It is used in fixed-dose combination with metformin for the treatment of **Type 2 diabetes**

**Rosiglitazone may be associated with an increased risk of cardiovascular adverse events; and continued use of this drug is questionable as its risk - benefit appears unfavourable and safer alternatives are available.**<sup>2</sup>

**Rosiglitazone has been suspended from the European and NZ markets due to its association with adverse cardiovascular events.**

In Australia it is only available in **fixed-dose combination** with **metformin**

Rosiglitazone has 2 important contraindications that its fellow glitazone, pioglitazone, does not appear to have, namely:

1. Treatment with insulin
  - The combination with rosiglitazone may *increase* the risk of heart failure and myocardial ischaemia.
2. Coronary heart disease:
  - Contraindicated in ACS due to the increased risk of developing heart failure and rosiglitazone’s association with cardiac ischaemic events.

Not recommended in ischaemic heart disease, particularly in patients taking nitrates, as rosiglitazone may increase risk of cardiac ischaemia.

**See also separate document on Metformin (in Drugs folder)**

### History

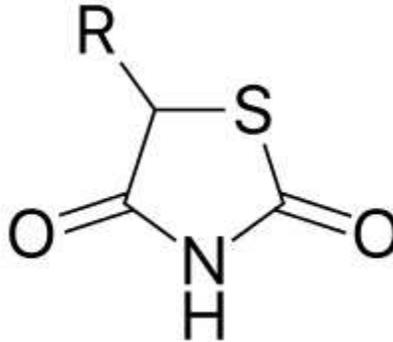
Ciglitazone was the prototype thiazolidinedione compound developed by the Japanese pharmaceutical company, Takeda Pharmaceuticals in the early 1980s. It was never introduced into clinical practice because of its toxicity in animals.

Other compounds including pioglitazone and **rosiglitazone** were subsequently developed with less toxicity that could be used in clinical practice.

Rosiglitazone was approved by the US FDA in 1999

## Chemistry

The **thiazolidinediones**, also known as **glitazones** after the prototypical drug ciglitazone are a class of heterocyclic compounds consisting of a five-membered C<sub>3</sub>NS ring



*The glitazone C<sub>3</sub>NS ring functional group*

## 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

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 SGLT2) inhibitors (or “Gliflozins”):**

*These agents reduce glucose reabsorption in the kidneys.*

*Examples include:*

- Dapagliflozin
- Empagliflozin

### Preparations

In Australia rosiglitazone is only available in **fixed-dose combination** with **metformin**

Rosiglitazone maleate and metformin hydrochloride as:

**Fixed-dose combinations tablets:**

- Rosiglitazone 2 mg + metformin 500 mg
- Rosiglitazone 2 mg + metformin 1000 mg
- Rosiglitazone 4 mg + metformin 500 mg
- Rosiglitazone 4 mg + metformin 1000 mg

### Mechanism of Action

Rosiglitazone is an oral thiazolidinedione anti-diabetic agent that depends **on the presence of insulin** for its unique mechanism of action.

Rosiglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output.

Unlike the sulfonylureas, pioglitazone is **not an insulin secretagogue**.

Pioglitazone is a potent and highly selective agonist for **PPAR gamma** receptors, (i.e. **peroxisome proliferator activated receptor gamma**) a group of intracellular **nuclear** receptors.

PPAR receptors are found in tissues important for **insulin action** such as:

- Adipose tissue
- Skeletal muscle
- Liver.

Activation of PPARgamma nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of **glucose** and **lipid metabolism**.

By binding avidly to **PPAR gamma** receptors in adipocytes to promote adipogenesis and fatty acid uptake (in peripheral but not visceral fat) thiazolidinediones will reduce circulating fatty acid concentrations and lipid availability in liver and muscle.

Thiazolidinediones favorably alter concentrations of the hormones secreted by adipocytes, particularly adiponectin. They **increase** total body fat and have mixed effects on circulating lipids.

By so doing these drugs can improve the patient's **sensitivity to insulin**.

Although the precise mechanism by which the thiazolidinediones improve insulin sensitivity is still not completely understood, a large part of their action is thought to be mediated via changes in body fat and its distribution.

Their action, in large part, is mediated by activation of PPAR $\gamma$  and involves redistribution of surplus fatty acids to peripheral (as opposed to visceral) fat. This reduces fatty acid availability in the circulation as well as in liver and muscle - thus improving insulin sensitivity.

### Pharmacodynamics

Rosiglitazone:

1. **Improves sensitivity to insulin in muscle and adipose tissue**
2. **Inhibits hepatic gluconeogenesis.**

The **decreased insulin resistance** produced by pioglitazone results in:

1. Lower blood glucose concentrations

2. Lower plasma insulin levels:
  - This which may be a consequence of improved insulin sensitivity and/or reduced circulating fatty acids (as fatty acids stimulate insulin secretion).
3. Lower HbA1c values.

**Additional** biological effects of the thiazolidinediones as a class include: <sup>5</sup>

1. Increased HDL cholesterol concentrations
2. Increased LDL cholesterol concentrations
3. Increased LDL cholesterol particle size
4. Reduced triglyceride concentrations (particularly pioglitazone)
5. Small reduction in blood pressure
6. Reduced incidence of microalbuminuria
7. Decrease in plasminogen activator inhibitor-1 and fibrinogen
8. Vasodilation/ Increased vascular reactivity
9. Anti-inflammatory effects

All of these effects, *except for increased LDL cholesterol* concentrations, would be regarded as **potentially beneficial** in regard to the metabolic syndrome and cardiovascular disease.

*Comparative information to Pioglitazone:* <sup>2</sup>

**Rosiglitazone may be associated with an increased risk of cardiovascular adverse events; continued use of this drug is questionable as its risk–benefit appears unfavourable and safer alternatives are available.**

Rosiglitazone is only available in combination with metformin.

Pioglitazone seems to have a better effect on the lipid profile than rosiglitazone and limited data suggest that it does not increase risk of cardiovascular ischaemic events.

Rosiglitazone and pioglitazone seem to have a similar effect on blood glucose control. Both drugs can cause weight gain, oedema and anaemia, and increase risk of heart failure and fractures.

## Pharmacokinetics

### Absorption:

- Rosiglitazone is administered orally.  
It is rapidly and completely absorbed after oral administration
- There is negligible first-pass metabolism.
- Absolute bioavailability of rosiglitazone following both a 4 and 8 mg oral doses is approximately 99%.

### Distribution

- The volume of distribution of rosiglitazone is approximately 0.184 L/kg
- Protein binding (primarily to albumin) is high at 99.8%
- Rosiglitazone can cross the human placenta.
- It is unknown if rosiglitazone is excreted in human breast milk.

### Metabolism and excretion:

- The metabolism of rosiglitazone is extensive with none of the parent compound being excreted unchanged.

The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. The metabolites of rosiglitazone are not considered to have any significant clinical effect.

Rosiglitazone is predominantly metabolised by cytochrome P450 (CYP) isoenzymes system.

- The elimination half-life is approximately 3 - 4 hours.

## Indications

Rosiglitazone is recommended in fixed-dose combination with metformin for the treatment of **Type 2 diabetes**

Currently, because of concerns about cardiac toxicity, it is mainly reserved for patients **unable to tolerate** other anti-diabetic drugs and who do not otherwise have specific contra-indications to rosiglitazone.

## Contra-indications/precautions

For the glitazones as a group:

1. Known hypersensitivity or allergy to rosiglitazone.
2. Ketoacidosis - contraindicated.
3. Type 1 diabetes - contraindicated.
4. Acute illness (e.g. coma, infection, trauma) - monitor blood glucose and test ketones; substitute insulin treatment if glycaemic control is inadequate.
5. Osteoporosis (or risk factors) - thiazolidinediones may increase risk of fracture.
6. Heart failure:

Thiazolidinediones may worsen heart failure.

- Rosiglitazone is contraindicated in patients with a history of heart failure.
  - **Pioglitazone** is contraindicated in NYHA class II–IV. Use cautiously in NYHA class I; start with a low dose and monitor carefully.
7. Hepatic:
    - Avoid use when aminotransferase levels are > 2.5 times upper limit of normal.
  8. There is some evidence that suggests pioglitazone may increase the risk of bladder cancer, particularly in patients treated for > 1 year.
    - Consider risk factors for bladder cancer (e.g. age, smoking, occupational chemical exposure, uninvestigated macroscopic haematuria) before starting treatment.

*Additional* precautions for **rosiglitazone** include:

1. Treatment with insulin
  - The combination with rosiglitazone may *increase* the risk of heart failure and myocardial ischaemia.
2. Coronary heart disease:
  - Contraindicated in ACS due to the increased risk of developing heart failure and rosiglitazone's association with cardiac ischaemic events.

Not recommended in ischaemic heart disease, particularly in patients taking nitrates, as rosiglitazone may increase risk of cardiac ischaemia.

### Pregnancy

Rosiglitazone is classified as category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There is limited published information available describing the use of rosiglitazone during the first trimester of pregnancy.

Rosiglitazone use in eight patients with polycystic ovarian syndrome, who were unable to tolerate metformin during their first 12 weeks of gestation, has been reported. All eight women delivered healthy infants with no observed congenital malformations.

Two other case reports of inadvertent exposure to rosiglitazone in the first or second trimester of pregnancy have been located. Both cases have resulted in normal pregnancy outcomes.

Dietary modification and insulin therapies are preferred during pregnancy. Follow-up and monitoring of both maternal and fetal wellbeing by a multidisciplinary team is recommended to ensure good glycaemic control and satisfactory fetal growth.

### Breast feeding

Reports describing the use of rosiglitazone during breastfeeding have not been located.

Due to potential adverse effects in the breastfed infant, consider an alternative treatment or avoid breastfeeding while undergoing rosiglitazone therapy.

### Adverse Effects

For the glitazones as a group these may include:

1. Myalgia / arthralgia
2. Fluid retention:
  - Peripheral oedema / weight gain
3. Fractures (including distal limb fractures in women)
4. Elevated liver enzymes

5. Worsening of heart failure heart failure
6. Macular oedema
7. Elevated creatine kinase levels.

*And for rosiglitazone specifically:*

8. The combination of **insulin** with rosiglitazone may *increase* the risk of heart failure and myocardial ischaemia.
9. In **ACS** there is an increased risk of developing heart failure
10. In **ischaemic heart disease**, particularly in patients taking nitrates, rosiglitazone may increase the risk of cardiac ischaemia.

### Dosing

Usual dosing in adults is:

- 1 tablet (of any strength) twice a day with or after food.

Usual initial dose is rosiglitazone 4 mg daily with current metformin dose.

Adjust dose according to response.

Wait 1 - 2 weeks after changing metformin dose and 6 - 8 weeks after changing rosiglitazone dose before further increasing the dose.

The maximum daily dose of rosiglitazone is 8 mg with metformin 2000 mg.

**Stop treatment if there is no effect after 6 months**

### Monitoring:

Monitor liver enzymes at baseline, then every 2 months for the first year.

Then periodically monitor or when clinically indicated; stop treatment if jaundice occurs or if ALT rises > 3 times ULN



*Triumphal Quadriga, c. 2nd-3rd century A.D, Roman bronzes, Museum of the Basilica of St Marks.*

*Perhaps the greatest symbol of the tragic sack of Constantinople by the Army of the Fourth Crusade are four bronze horses known as the Triumphal Quadriga. They are a set of Roman bronze statues originally part of a monument depicting a quadriga, or a four horse-led racing chariot. They are thought to date from the Second or Third century A.D and were later taken to the Hippodrome at Constantinople. Following the destruction of Constantinople the Venetians took them as loot back to Venice where they were placed on the loggia above the great balcony, of St Mark's Basilica. There they stood for almost six centuries, until 1797 when the thousand year old Republic fell to Napoleon Bonaparte. Napoleon looted the city of its greatest Art treasures, among these were the four bronze horses which were taken to Paris. Venetians were outraged, though they could hardly complain, they had after all stolen them as loot during the sack of Constantinople in the early Thirteenth century. With the final defeat of Napoleon in 1815, the horses were returned to the St. Marks. In the late 1980s, the horses were moved to the gallery of the Basilica Museum, victims of the Twentieth century pollution that had begun*

*to take an even more terrible toll of Venetian sculpture than Napoleon ever did. Replicas now reside on the loggia where the originals had stood for over half a millennium.*



*The last of the original four bronze horses of Constantinople to stand over the loggia of St Marks, (the three other originals have been moved to the Basilica Museum). (Author's photograph, 1981).*

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