3. DRUG AND EXCIPIENT PROFILE

3.1 DRUG PROFILE-PIOGLITAZONE
(Pioglitazone monographs Mosby’s Drug consult 2005)

a. Chemical Name: (±)-5-[p-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione monohydrochloride

b. Chemical Formula: C_{19}H_{20}N_{2}O_{3}S.HCL

c. Chemical Structure:

\[ \text{Chemical Structure Image} \]

d. Molecular Wt.: 392.90

e. Half life: 3-7 hours

f. Dose: Initially, 15 or 30 mg once daily. If response is inadequate, increase dosage in increments, up to a maximum dosage of 45 mg daily. If response is inadequate with monotherapy, consider combination therapy.

g. Bioavailability: 83%

Category: Pioglitazone is highly selective agonist for peroxisome proliferator activated receptor –gamma (PPARγ) for this reason Pioglitazone is an oral antidiabetic agent that acts primarily by decreasing insulin resistance

h. Pharmacology:

Pioglitazone is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, Pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome
proliferators - activated receptor- gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

i. **Pharmacokinetics**

**Absorption**: Absorbed quickly. Food delays the time but not the extent of absorption.

**Distribution**: Parent compound and metabolites are extensively protein bound (>99%) primarily to serum albumin.

**Metabolism**: Extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites are pharmacologically active in animal models. *In vitro* data demonstrate that multiple CYP isoforms are involved in the metabolism including CYP2C8 and, to a lesser degree, CYP3A4.

**Elimination**: 15-30% of the dose is recovered in the urine as the metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

j. **Adverse Reactions**: The most common adverse reactions (>10%) include: weight gain and upper respiratory tract infection. Less common adverse reactions (1%-10%) include: edema, headache, fatigue, hypoglycemia, anemia, myalgia, sinusitis, pharyngitis. Serious but life threatening adverse reactions include: CHF, dyspnea, hepatic failure, hepatitis, increased CPK or liver transaminase levels
3.2 DRUG PROFILE OF ROSIGLITAZONE (Pedro Iglesias et al 2006)

a. Chemical Name: \((RS)-5-[4-(2-[methyl\ (pyridin-amino\) ethoxy) benzyl] thiazolidine-2,4-dione maleate

b. Chemical Formula: C18H19N3O3S, C4H4O4

c. Chemical Structure:

![Chemical Structure Diagram]

d. Molecular Wt.: 473.5

e. Half life: 3-4 hours

f. Dose: 8-15 mg

g. Bioavailability: 99%

h. Category: Rosiglitazone is oral hypoglycemic agent in the thiazolidinedione class of drug. It works as an insulin sensitizer, by binding to the pPAR receptor in fat cell and making the cells more responsive to insulin\(^{121}\)

i. Pharmacology

Rosiglitazone is a member of the thiazolidinedione class of drugs. Thiazolidinediones act as insulin sensitizers. They reduce glucose, fatty acid, and insulin blood concentrations. They work by binding to the peroxisome proliferator-activated receptors (PPARs). PPARs are receptors on the membrane of the cell nucleus. Thiazolidinediones enter the cell, bind to the nuclear receptors, and affect the expression of DNA. There are several PPARs, including PPAR\(\alpha\), PPAR\(\beta/\delta\), and PPAR\(\gamma\). Thiazolidinediones bind to PPAR\(\gamma\).

j. Pharmacokinetic

The absorption of rosiglitazone was rapid and essentially complete, with absolute bioavailability estimated to be \(~99\%\) after oral tablet dosing and \(~95\%\) after oral solution dosing, and clearance was primarily metabolic. The time to maximal concentration of radioactivity and the elimination half-life for two metabolites in plasma were
significantly longer than for rosiglitazone itself (4–6 h versus 0.5–1 h, and ca. 5 days versus 3–7 h). The major routes of metabolism were N-demethylation and hydroxylation with subsequent conjugation, of which neither was affected by the route of drug administration. Rosiglitazone was well tolerated in all formulations.

**k. Adverse reaction**

The most common adverse reactions anemia and edema these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone. Less common adverse reactions include headache, hypoglycemia, myalgia, sinusitis, pharyngitis. Serious but life threatening adverse reactions include: CHF, dyspnea, hepatic failure.
3.3 EXCIPIENT PROFILE

**Poloxamer** (Rowe R.C et al n.d)

**a. Synonyms** Lutrol; Monolan; Pluronic; poloxalkol; polyethylene–propylene glycol copolymer; polyoxyethylene–polyoxypropylene copolymer; Supronic; Synperonic.

**b. Chemical Name** \( \alpha \)-Hydro-\( \omega \)-hydroxypoly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymer

**c. Empirical Formula** The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula \( \text{HO(C}_2\text{H}_4\text{O})_a(C_3\text{H}_6\text{O})_b(C_2\text{H}_4\text{O})_a\text{H.} \)

**d. Molecular wt.** Poloxamer 188 – 7680-9510

Poloxamer 407 - 9840-14600

**e. Structural Formula:**

**f. Functional Category**
Dispersing agent, emulsifying and coemulsifying agent, solubilizing agent, tablet lubricant, wetting agent.

**g. Applications in Pharmaceutical Formulation or Technology** (Suh H et al 1996)

Poloxamer are nonionic polyoxyethylene–polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available. Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings. Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes and in the preparation of solid-dispersion system.