1.3 Product information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

SUMMARY OF PRODUCTS CHARACTERISTICS

1. Name of the medicinal product

1.1 Product name:
PIO-GLUCODIX-15
(PIOGLITAZONE HCl AND METFORMIN HCl TABLET)

1.2 Strength:
Each film coated tablet contains:
Pioglitazone HCl BP
Eq. to Pioglitazone 15 mg
Metformin HCl BP 500 mg
Excipients Q.S.
Colour: Iron Oxide Yellow

1.3 Pharmaceutical dosage forms:
Film coated Tablet

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Label Claim (mg)	Actual Qty/Tab. (mg)	Actual Qty/batch (kg)	Function
Mixing-I					
1.	Metformin Hydrochloride BP	500.000	500.000	50.000	Type-II Antidiabetic
2.	Calcium Hydrogen Phosphate BP	-	98.664	9.866	Diluent
3.	Maize Starch BP**	-	68.900	6.890	Diluent
4.	Croscarmellose Sodium BP	-	7.800	0.780	Disintegrant
Binding I					
5.	PVP K-30 BP	-	22.000	2.200	Binder
6.	Purified Water BP***	-	Q.S	Q.S	Solvent
Mixing-II					
7.	Pioglitazone Hydrochloride BP Eq. to Pioglitazone*	15.000	16.530	1.653	Type-II Antidiabetic
8.	Lactose BP**	-	65.000	6.500	Diluent
9.	Microcrystalline Cellulose BP	-	7.300	0.730	Diluent
Binding II					
10	Hydroxy Propyl Cellulose BP	-	4.000	0.400	Binder
11	Purified Water BP***	-	Q.S	Q.S	Solvent
Lubrication					
12	Purified Talc BP		4.000	0.400	Glidant
13	Sodium Starch Glycolate BP		8.200	0.820	Disintegrant
14	Croscarmellose Sodium BP		12.000	1.200	Disintegrant
15	Colloidal Anhydrous Silica BP		5.000	0.500	Glidant
16	Magnesium Stearate BP		2.000	0.200	Lubricant
Total weight of Uncoated tablets			**821.394 mg**	**82.139 Kg**	-
Film coating					
17	Colorezy White 17F580001 IH		28.500	2.850	Film former
18	Iron Oxide Yellow IH		0.106	0.011	Colorant

19	Isopropyl Alcohol BP***		0.02 ml	2.12 Lit.	Solvent
20	Methylene Chloride BP***		0.03 ml	3.18 Lit.	Solvent
Total weight of Film coated tablets			**850.000 mg**	**85.000 kg**	

*Quantity to be calculated on the basis of its potency

Calculation of Pioglitazone HCL BP Eq. to Pioglitazone 15.000 mg (100% Potency)

$$= \frac{\text{Label claim} \times \text{molecular weighr of Pioglitazone HCL} \times 100}{(\text{Molecular Weight of Pioglitazone}) \times \text{Potency}}$$

$$= \frac{15 \times 392.90 \times 100}{356.4387 \times 100}$$

$$= 16.534 \text{ mg}$$

** Quantity to be compensates on increasing quantity of active material.
*** The materials that will not remain in the final product.

3. Pharmaceutical forms

Oral Film coated Tablet

4. Clinical Particulars

4.1 Therapeutic Indications

As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and metformin or who have inadequate glycemic control on a thiazolidinedione alone or metformin alone.

4.2 Posology and Method of administration

Adults

PO Starting dose is based on patient's current regimen of pioglitazone and/or metformin.
Immediate Release Pioglitazone 30 mg/metformin 500 mg once or twice daily with food, not to exceed pioglitazone 90 mg/metformin 2,550 mg per day.

General Advice

- Administer with food.
- ER tablets must be swallowed whole and not chewed, crushed, or cut.
- Elderly, debilitated, and malnourished patients should not be titrated to the maximum dose.
- Do not initiate treatment if a patient exhibits clinical evidence of active liver disease or increased serum transaminase levels at the start of therapy.

Method of Administration:

Oral administration

4.3 Contraindications

It is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients
- Cardiac failure or history of cardiac failure (NYHA stages I to IV)
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria

- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock
- Hepatic impairment
- Acute alcohol intoxication, alcoholism
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 mL/min)
- Acute conditions with the potential to alter renal function such as:
  - Dehydration
  - Severe infection
  - Shock
- Intravascular administration of iodinated contrast agents
- Breast-feeding

4.4 Special warning and precaution for use

Congestive heart failure

Pioglitazone may cause or exacerbate CHF in some patients. Observe patients carefully for signs or symptoms of heart failure after starting or increasing the dose of pioglitazone. If signs or symptoms develop, manage the heart failure according to the current standards of care. Also, consider discontinuation or dose reduction of pioglitazone. Treatment with pioglitazone is not recommended in patients with symptomatic heart failure. Use in patients with established NYHA class III or IV heart failure is contraindicated.

Lactic acidosis

Lactic acidosis can occur because of metformin accumulation. Risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute CHF. The onset is often subtle with symptoms such as malaise, myalgias, respiratory distress, somnolence, nonspecific abdominal distress, and laboratory abnormalities such as low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, discontinue the medication and hospitalize the patient immediately.

Pregnancy

Category C

Lactation

Undetermined.

Children

Safety and efficacy not established.

Elderly

Ensure that initial and maintenance doses are conservative because of the potential for reduced renal function; avoid titration to maximum dose.

Renal Function

Risk of metformin accumulation and lactic acidosis increases with degree of renal function impairment. Patients with serum creatinine levels above the ULN for their age should not receive metformin-containing products.

Hepatic Function

Do not initiate therapy in patients with clinical evidence of active liver disease or baseline ALT more than 2.5 × ULN. Initiate or continue therapy in patients with mildly elevated liver enzymes (ALT less than 2.5 × ULN) with caution; discontinue therapy in these patients if ALT increases to more than 3 × ULN and persists, or if the patient develops jaundice.

Special Risk Patients

Do not titrate elderly, debilitated, and malnourished patients to the maximum dose. Do not initiate treatment if a patient exhibits clinical evidence of active liver disease or increased serum transaminase levels at the start of therapy.

Edema
Pioglitazone may cause fluid retention. Use with caution in patients with edema or at risk of heart failure.
Fractures
Increased incidence of bone fracture has been observed in women taking pioglitazone.
Hematologic
Decreases in Hgb (2% to 4%) have been reported in patients receiving pioglitazone.
Hypoglycemia
Risk of hypoglycemia increases when used with other oral hypoglycaemic agents or insulin; reduction in the dose of the concomitant agent may be necessary.
Type 1 diabetes
Do not use in these patients.
Intravascular iodinated contrast materials
Can lead to acute alteration of renal function and have been associated with metformin-induced lactic acidosis. Temporarily discontinue pioglitazone/metformin prior to the procedure, and withhold for 48 h after the procedure; restart only after renal function has returned to normal.
Loss of glucose control
Consider temporarily withholding therapy and administering insulin in patients who lose glycemic control as result of fever, trauma, infection, or surgery.
Macular edema
Has been reported during post marketing experience.
Ovulation
Pioglitazone therapy may result in resumption of ovulation in premenopausal an ovulatory women with insulin resistance. Consider contraceptive measures in such patients.
Surgical procedures
Temporarily suspend therapy for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). Do not restart until patient's oral intake has resumed and renal function has been evaluated as healthy.
Urinary bladder tumors
Do not use in patients with active bladder cancer. Evaluate benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone/metformin use in patients with a history of bladder cancer.
Vitamin B 12 levels
Metformin may interfere with B 12 absorption from the B 12 -intrinsic factor complex.
Weight gain
Dose-related weight gain has been reported. Assess patients who experience unusually rapid increases in weight for fluid accumulation and volume-related events (eg, edema, heart failure).

4.5 Paediatric population
Not applicable

4.6 Interaction with other medicinal products and other forms of interactions
Alcohol
Effect of metformin on lactate metabolism may be potentiated. Warn patients against excessive alcohol intake, short- or long-term, while receiving metformin.
Atorvastatin
Concurrent use may decrease pioglitazone and atorvastatin serum concentrations. Coadminister with caution.
Cationic drugs (eg, amiloride, digoxin, quinidine)
May increase metformin serum levels by competing for tubular secretion. Careful patient monitoring and dose adjustment of metformin and/or the interfering drug are recommended

in patients who are taking cationic medications excreted via the proximal renal tubular secretory system.

Cimetidine

Metformin serum levels may be elevated, increasing pharmacologic effects and adverse reactions. Closely monitor renal function. Metformin dosage reduction may be needed.

CYP2C8 inducers (eg, rifamycins [eg, rifabutin, rifampin, rifapentine])

Rifampin administration may reduce plasma concentrations and half-life while increasing Cl of pioglitazone, possibly resulting in decreased glycemic control. Closely monitor blood glucose concentrations when starting or stopping CYP2C8 inducers.

CYP2C8 inhibitors (eg, fluvoxamine, gemfibrozil, ketoconazole, trimethoprim)

Inhibition of pioglitazone metabolism. Plasma concentration of pioglitazone may be elevated, increasing hypoglycemic and other adverse reactions (eg, edema). Closely monitor blood glucose concentrations when starting or stopping CYP2C8 inhibitors.

CYP3A4 substrates

Pioglitazone may be a weak inducer of CYP3A4, which may decrease serum levels of other drugs metabolized by this isozyme.

Drugs that cause hyperglycemia (eg, calcium channel blockers, corticosteroids, diuretics, estrogens, isoniazid, nicotinic acid, oral contraceptives, phenothiazines, phenytoin, sympathomimetics, thyroid products)

May lead to loss of glycemic control. Closely monitor the patient to maintain adequate glycemic control.

Furosemide

May increase metformin serum levels; metformin may reduce furosemide levels. Coadminister with caution and closely monitor the patient.

Hormonal contraceptives

Coadministration of pioglitazone with a hormonal contraceptive (ie, ethinyl estradiol/norethindrone) decreased the ethinyl estradiol AUC and C_{max}. The clinical relevance is unknown.

Insulin

Risk of edema may be increased, even after several months of combined therapy.

Iodinated contrast material

May cause acute renal failure and has been associated with lactic acidosis in patients receiving metformin. Withhold pioglitazone/metformin therapy prior to and for 48 h after procedures using iodinated contrast material.

Midazolam

Midazolam C_{max} and AUC may be reduced, decreasing the pharmacologic effect.

4.7 Additional information on special populations

Not Applicable

4.8 Fertility, pregnancy and lactation

Use is not recommended; this drug should not be used during pregnancy unless the benefit outweighs the risk to the fetus. Comments: Premenopausal anovulatory women may be at risk for pregnancy; these women should be informed of pregnancy risk. US FDA pregnancy category: C

Animal studies using pioglitazone at 10 to 40 times the maximum recommended human dose have shown increased rates of postimplantation loss, delayed development, reduced fetal weights, and delayed parturition. There are no adequate and well-controlled studies in pregnant women. Abnormal blood glucose concentrations during pregnancy are associated with a higher incidence of congenital anomalies, increased neonatal morbidity, and mortality. Most experts recommend insulin use during pregnancy to maintain blood glucose concentrations as close to normal as possible. US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and

well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Metformin / pioglitazone Breastfeeding Warning

UK: Use is contraindicated. US: A decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother. Excreted into human milk: Yes, in small amounts (metformin); Unknown (pioglitazone) Excreted into animal milk: Yes (metformin); Yes (pioglitazone) Comments: The effects in the nursing infant are unknown.

4.9 Effects on ability to drive and use machines

Patients should be warned that visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting.

4.10 Undesirable effects

Very Common: Abdominal pain, Diarrhea, Loss of Appetite, Nausea, Vomiting, etc.

Common: Upper respiratory Tract Infections, Anaemia, Hypo-aesthesia, Headache, Taste Disturbance, Visual Disturbance, Bone Fracture, Arthralgia, Haematuria, Erectile Dysfunction, Oedema, Weight gain, etc.

Uncommon: flatulence, insomnia, bladder cancer, sinusitis, etc.

Very rare: Vitamin B12 absorption decreased, lactic acidosis, erythema, Pruritis, Urticaria, etc.

Not known: hypersensitivity and allergic reactions, macular oedema, Hepatitis, alanine aminotransferase increased, liver function tests abnormal, etc.

4.11 Overdose

No data are available with regard to overdose of Competent.

In clinical studies, patients have taken pioglitazone at higher than the recommended highest dose of 90 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms.

A large overdose of metformin (or coexisting risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs

ATC code: A10BD05

Mechanism of action:

Pioglitazone and metformin hydrochloride tablets combine two antidiabetic medications with different mechanisms of action to improve glycemic control in adults with type 2 diabetes: pioglitazone, a thiazolidinedione, and metformin hydrochloride, a biguanide. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose production.

Pioglitazone

Pioglitazone is a thiazolidinedione 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. Pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-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.
In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.
Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.
Metformin Hydrochloride
Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or healthy subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacokinetic Properties

Absorption
Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2-60 mg. Steady state is achieved after 4-7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80%.
Distribution
The estimated volume of distribution in humans is 0.25 L/kg.
Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99%).
Biotransformation
Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of pioglitazone, whilst the relative efficacy of M-II is minimal.
In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man.
Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of pioglitazone (see section 4.5).
Elimination
Following oral administration of radiolabelled pioglitazone to man, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean plasma elimination half-life of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Metformin

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63-276 L.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical Safety data

Pioglitazone

In toxicology studies, plasma volume expansion with haemodilution, anaemia, and reversible eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs, and monkeys. In addition, increased fatty deposition and infiltration were observed. These findings were observed across species at plasma concentrations ≤ 4 times the clinical exposure. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

Pioglitazone was devoid of genotoxic potential in a comprehensive battery of *in vivo* and *in vitro* genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

Metformin

Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. Pharmaceutical Particulars

6.1 List of Excipients

Dibasic Calcium Phosphate Anhydrous
Maize Starch
Croscarmellose Sodium
Lactose
Microcrystalline Cellulose Phosphate
Povidone
Purified Water
Hydroxy Propyl Cellulose
Purified Talc
Sodium Starch Glycolate
Colloidal Anhydrous Silica
Magnesium Stearate
Colorezy White
Iron Oxide Red
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

Not known.

6.3 Shelf Life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

10 X 10 Tablets in Alu-Alu Blister Pack

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder

Name : Stallion Laboratories Pvt. Ltd.
Address : C-1B, 305/2, 3, 4& 5, G.I.D.C.
Kerala (Bavla), Dist.: Ahmedabad, Gujarat, India.
Phone : (02714)-268315, 268386
Fax : (02714)-268769
E-mail : info@stallionlabs.com

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

STALLION LABORATORIES PVT. LTD. INDIA