1. Name of the medicinal product:

ZIVASTA 30 MG TABLET
(Pioglitazone Tablets USP 30 mg)

2. Qualitative and quantitative composition:
Each uncoated tablet contains:
-Pioglitazone Hydrochloride USP Equivalent to Pioglitazone (30 mg)
- Approved colour used. (-)
- Excipients (QS)

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason For Function
a)	**Dry Mixing**					
1.	Lactose Monohydrate	BP	NA	NA	82.00	Diluent
b)	**Binder Preparation**					
2.	Povidone (K 30)	BP	NA	NA	2.00	Binder
3.	Macrogol 6000	BP	NA	NA	4.00	Plasticizer
4.	Polysorbate 80	BP	NA	NA	4.00	Solubilizing agent
5.	Methyl hydroxybenzoate	BP	NA	NA	0.50	Preservative
6.	Propyl hydroxybenzoate	BP	NA	NA	0.25	Preservative
7.	Purified water	BP	NA	NA	-----	Vehicle
c)	**Lubrication**					
8.	Pioglitazone Hydrochloride	USP	Pioglitazone Hydrochloride USP Equivalent to Pioglitazone (30 mg)	NA	33.07	Active
9.	Sodium Starch Glycolate	BP	NA	NA	10.00	Disintegrant
10.	Croscarmellose Sodium	BP	NA	NA	10.00	Disintegrant
11.	Colloidal Anhydrous silica	BP	NA	NA	1.00	Glidant
12.	Magnesium stearate	BP	NA	NA	3.00	Lubricant
13.	Titanium Dioxide	BP	NA	NA	0.18	Colour
	Average weight of film coated tablet (In mg)				**150.00**	

3. Pharmaceutical form: Film coated tablets
Description: White coloured, round shaped, biconvex, uncoated tablet plain on both sides.

4. Clinical Particulars
4.1 Therapeutic indications
ZIVASTA 30 MG TABLET (Pioglitazone Tablets USP 30 mg) is indicated as second or third line in the treatment of type 2 diabetes mellitus as described below:
- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance
Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.
After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

4.2 Posology and method of administration

Posology

Pioglitazone treatment may be initiated at 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily.

In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of insulin should be decreased.

Elderly

No dose adjustment is necessary for elderly patients. Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin.

Renal impairment

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min). No information is available from dialysed patients therefore pioglitazone should not be used in such patients.

Hepatic impairment

Pioglitazone should not be used in patients with hepatic impairment.

Paediatric population

The safety and efficacy of pioglitazone in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

For oral use.

Pioglitazone tablets are taken orally once daily with or without food. Tablets should be swallowed with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- you have heart failure or have had heart failure in the past,
- you have liver disease,
- you have had diabetic ketoacidosis (a complication of diabetes causing rapid weight loss,
- nausea or vomiting),
- you have or have ever had bladder cancer,
- you have blood in your urine that your doctor has not checked.

4.4 Special warnings and precautions for use

Fluid retention and cardiac failure:

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema. Post marketing cases of peripheral oedema and cardiac failure have also been reported in patients with concomitant use of pioglitazone and non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

Elderly

Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.

In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

Bladder Cancer
Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study medicinal product was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, although not all studies identified a statistically significant increased risk.
Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.
Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.
Monitoring of liver function
There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section 4.8). It is recommended, therefore, that patients treated with pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with pioglitazone in all patients. Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 X upper limit of normal) or with any other evidence of liver disease.
Following initiation of therapy with pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 X upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, the medicinal product should be discontinued.
Weight gain
In clinical trials with pioglitazone there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.
Haematology
There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with haemodilution. Similar changes were seen in metformin (haemoglobin 3 - 4% and haematocrit 3.6 – 4.1% relative reductions) and to a lesser extent sulfonylurea and insulin (haemoglobin 1 – 2 % and haematocrit 1 – 3.2% relative reductions) treated patients in comparative controlled trials with pioglitazone.
Hypoglycaemia
As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulfonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulfonylurea or insulin may be necessary.
Eye disorders
Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

4.5 Interaction with other medicinal products and other forms of interaction
Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulfonylureas does not appear to affect the pharmacokinetics of the sulfonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these

enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4). Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding

Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

Pioglitazone has no or negligible influence on the ability to drive and use machines. However, patients who experience visual disturbance should be cautious when driving or using machines.

4.8 Undesirable effects

Like all medicines, this medicine can cause side-effects although not everybody gets them.

If you notice any of the following side effects, stop taking this medicine and contact your doctor or go to the nearest hospital casualty department straight away.

-Heart failure (when taking pioglitazone in combination with insulin): symptoms are unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

-Bladder cancer: signs and symptoms include blood in your urine, pain when urinating or a sudden need to urinate.

- Localised swelling (oedema) (when taking pioglitazone in combination with insulin).

-Broken bones (this has been reported in both female and male patients).

-Blurred vision due to swelling (or fluid) at the back of the eye. Also, if you already have blurred vision and the symptom gets worse, talk to your doctor as soon as possible.

-Allergic reactions: symptoms of a serious allergic reaction include hives and swelling of the face, lips, tongue, or throat that may cause difficulty in breathing or swallowing

Common: may affect up to 1 in 10 people

abnormal vision
respiratory infection
weight gain
numbness

Uncommon: may affect up to 1 in 100 people

inflammation of the sinuses (sinusitis)
difficulty sleeping (insomnia).

Not known: frequency cannot be estimated from the available data

Increase in liver enzymes
allergic reactions

The following additional side effects have been experienced by some patients when Pioglitazone is taken with other antidiabetic medicines.

Very common: may affect more than 1 in 10 people)

decreased blood sugar (hypoglycemia)

Common: may affect up to 1 in 10 people
headache
dizziness
joint pain
impotence
back pain
shortness of breath
small reduction in red blood cell count (anemia)
flatulence
increase in enzyme levels
Uncommon: may affect up to 1 in 100 people
sugar in urine, proteins in urine
spinning sensation (vertigo)
sweating
tiredness
increased appetite

4.9 Overdose
In clinical studies, patients have taken pioglitazone at higher than the recommended highest dose of 45 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.
Hypoglycaemia may occur in combination with sulfonylureas or insulin. Symptomatic and general supportive measures should be taken in case of overdose.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins; Thiazolidinediones; ATC code: A10BG03.

Mechanism of action
Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

Clinical efficacy and safety
Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of HbA1c ≥ 8.0 % after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in patients treated with gliclazide, compared with pioglitazone. At two years, glycaemic control (defined as HbA1c < 8.0 %) was sustained in 69 % of patients treated with pioglitazone, compared with 50 % of patients on gliclazide.
In a two-year study of combination therapy comparing pioglitazone with gliclazide when added to metformin, glycaemic control measured as mean change from baseline in HbA1c was similar between treatment groups after one year. The rate of deterioration of HbA1c during the second year was less with pioglitazone than with gliclazide.
In a placebo controlled trial, patients with inadequate glycaemic control despite a three month insulin optimisation period were randomised to pioglitazone or placebo for 12 months. Patients receiving pioglitazone had a mean reduction in HbA1c of 0.45 % compared with those continuing on insulin alone, and a reduction of insulin dose in the pioglitazone treated group.
HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. Two-year clinical studies have shown maintenance of this effect.
In one year clinical trials, pioglitazone consistently gave a statistically significant reduction in the albumin/creatinine ratio compared to baseline.
The effect of pioglitazone (45 mg monotherapy vs. placebo) was studied in a small 18-week trial in type 2 diabetics. Pioglitazone was associated with significant weight gain. Visceral fat was significantly decreased,

while there was an increase in extra-abdominal fat mass. Similar changes in body fat distribution on pioglitazone have been accompanied by an improvement in insulin sensitivity. In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo, with small, but not clinically significant increases in LDL-cholesterol levels.
In clinical trials of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL cholesterol levels compared with placebo, whilst reductions were observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced post prandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone's effects on glycaemia and were statistically significantly different to glibenclamide.
In PROactive, a cardiovascular outcome study, 5238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease were randomised to pioglitazone or placebo in addition to existing antidiabetic and cardiovascular therapy, for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulfonylurea. To be eligible patients had to have had one or more of the following: myocardial infarction, stroke, percutaneous cardiac intervention or coronary artery bypass graft, acute coronary syndrome, coronary artery disease, or peripheral arterial obstructive disease. Almost half of the patients had a previous myocardial infarction and approximately 20% had had a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were receiving cardiovascular medicinal products (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates).
Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing pioglitazone in all subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

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.

Elderly

Steady state pharmacokinetics are similar in patients age 65 and over and young subjects.

Patients with renal impairment

In patients with renal impairment, plasma concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but oral clearance of parent substance is similar. Thus free (unbound) pioglitazone concentration is unchanged.

Patients with hepatic impairment

Total plasma concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of pioglitazone.

5.3 Preclinical safety data

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.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

In an animal model of familial adenomatous polyposis (FAP), treatment with two other thiazolidinediones increased tumour multiplicity in the colon. The relevance of this finding is unknown.

Environmental Risk Assessment (ERA):

No environmental impact is anticipated from the clinical use of pioglitazone.

6 Pharmaceutical particulars

6.1 List of excipients

Lactose Monohydrate, Povidone (K 30), Macrogol 6000, Polysorbate 80, Methyl hydroxybenzoate, Propyl hydroxybenzoate, Purified water, Sodium Starch Glycolate, Croscarmellose Sodium, Colloidal Anhydrous silica, Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in cool, dry place. Store below 30°C.

Keep all medicines out of the reach of children.

Read leaflet carefully before use.

6.5 Nature and contents of container
Primary packing: 10 Tablets in an ALU-PVC blister.
Secondary packing: 3 Blisters are packed in a carton along with leaflet.
Tertiary packing: Shrink such 10 cartons. Such 24 Shrinks are packed in a 5 Ply shipper sealed with BOPP tape & strap with strapping roll.

6.6 Special precautions for disposal and other handling
None

7. Applicant / Manufacturer
Applicant

Applicant name and address	**M/s. EDEN U-K PHARM LTD.** J116, Daminja Avenue Housing Estate, Fegge, Anambra State
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
Contact person's phone number	+91 7350864803
Contact person's email	pravin.patil@kamlagroup.co.in