ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Glubrava 15 mg/850 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg of pioglitazone (as hydrochloride) and 850 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

The tablets are white to off-white, oblong, film-coated, embossed '15 / 850' on one face and '4833M' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glubrava is indicated as second line treatment of type 2 diabetes mellitus adult patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.

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 HbA_{1c}). 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 (see section 4.4).

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR ≥ 90 mL/min)
The recommended dose of Glubrava is 30 mg/day pioglitazone plus 1,700 mg/day of metformin hydrochloride (this dose is achievable with one tablet of Glubrava 15 mg/850 mg, taken twice a day).

Dose titration with pioglitazone (added to the optimal dose of metformin) should be considered before the patient is switched to Glubrava.

When clinically appropriate, direct change from metformin monotherapy to Glubrava may be considered.

Special populations
Elderly
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Glubrava should have their renal function monitored regularly (see sections 4.3 and 4.4).

Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).

Renal impairment
A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.
If no adequate strength of Glubrava is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	Metformin	Pioglitazone
60-89	Maximum daily dose is 3,000 mg Dose reduction may be considered in relation to declining renal function.	No dose adjustment. Maximum daily dose is 45 mg
45-59	Maximum daily dose is 2,000 mg The starting dose is at most half of the maximum dose.	
30-44	Maximum daily dose is 1,000 mg. The starting dose is at most half of the maximum dose.	
< 30	Metformin is contra-indicated	

Hepatic impairment
Glubrava should not be used in patients with hepatic impairment (see sections 4.3 and 4.4).

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

Method of administration

Tablets should be swallowed with a glass of water. Taking Glubrava with, or just after food, may reduce gastrointestinal symptoms associated with metformin.

4.3 Contraindications

Glubrava is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- 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 (see section 4.4)
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

There is no clinical experience of pioglitazone in triple combination with other oral antidiabetic medicinal products.

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever, heat, reduced fluid intake), Glubrava should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs)) should be initiated with caution in metformin treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Glubrava and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting treatment with a NSAID.

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. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration of insulin and Glubrava 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 nonsteroidal

anti-inflammatory drugs, including selective COX-2 inhibitors. Glubrava 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 12,506 patients, 0.15%) than in control groups (7 cases from 10,212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, p=0.029). After excluding patients in whom exposure to study drug 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 elevated liver enzymes and hepatocellular dysfunction during post-marketing experience with pioglitazone (see section 4.8). Although in very rare cases fatal outcome has been reported, causal relationship has not been established.
It is recommended, therefore, that patients treated with Glubrava undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Glubrava in all patients. Therapy with Glubrava 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 Glubrava, it is recommended that liver enzymes be monitored periodically according to clinical judgement. If ALT levels are increased to 3 x upper limit of normal during Glubrava 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 Glubrava 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.

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) treated patients in comparative controlled trials with pioglitazone.

Hypoglycaemia

Patients receiving pioglitazone in dual oral therapy with a sulphonylurea may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea 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.

Surgery

As Glubrava contains metformin hydrochloride, it must be discontinued at the time of surgery under general, spinal or epidural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Glubrava should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

Polycystic ovarian syndrome

As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued (see section 4.6).

Others

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomised, controlled, double blind clinical trials (see section 4.8).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed

excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women. The risk of fractures should be considered in the long term care of patients treated with pioglitazone (see section 4.8).

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section 4.5).

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Glubrava. The following statements reflect the information available on the individual active substances (pioglitazone and metformin).

Pioglitazone

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 (see section 4.4).

Glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dose of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Angiotensin-converting enzyme (ACE) inhibitors may decrease the blood glucose levels. If necessary, the dose of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. 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.

Metformin

Concomitant use not recommended
Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Glubrava must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

Combinations requiring precautions for use
Some medicinal products that can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDS, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with Glubrava, close monitoring of renal function is necessary.

Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Glubrava is not recommended in women of childbearing potential not using contraception. If a patient wishes to become pregnant, treatment with Glubrava should be discontinued.

Pregnancy

Pioglitazone
There are no adequate human data from the use of pioglitazone in pregnant women. Studies of pioglitazone in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Metformin
There are limited amount of data from the use of metformin in pregnant women. Animal studies have not revealed teratogenic effects or do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Glubrava should not be used during pregnancy. If a pregnancy occurs, treatment with Glubrava should be discontinued.

Breast-feeding

It is unknown whether pioglitazone and metformin are excreted in human milk. Available toxicological data in animals have shown excretion of pioglitazone and metformin in the milk of lactating rats (see section 5.3). A risk to the newborns/infants cannot be excluded.

Glubrava is contraindicated during breast-feeding (see section 4.3).

Fertility

In animal fertility studies with pioglitazone, there was no effect on copulation, impregnation or fertility index.
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machines

Glubrava 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

Summary of the safety profile

Clinical trials have been conducted with Glubrava tablets and co-administered pioglitazone and metformin (see section 5.1). At the initiation of the treatment abdominal pain, diarrhoea, loss of appetite, nausea and vomiting may occur, these reactions are very common but usually disappear spontaneously in most cases. Lactic acidosis is a serious reaction which may occur very rarely (< 1/10,000) (see section 4.4) and other reactions such as bone fracture, weight increase and oedema may occur commonly (≥ 1/100 to < 1/10) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported in double-blind studies and post-marketing experience are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing incidence followed by decreasing seriousness.

Adverse reaction	**Frequency of adverse reactions**		
	Pioglitazone	**Metformin**	**Glubrava**
Infections and infestations			
upper respiratory tract infection	common		common
sinusitis	uncommon		uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
bladder cancer	uncommon		uncommon
Blood and lymphatic system disorders			
anaemia			common
Immune System Disorders			
hypersensitivity and allergic reactions[1]	not known		not known
Metabolism and nutrition disorders			
Vitamin B12 absorption decreased[2]		very rare	very rare
lactic acidosis		very rare	very rare
Nervous system disorders			
hypo-aesthesia	common		common
insomnia	uncommon		uncommon
headache			common
taste disturbance		common	common
Eye disorders			
visual disturbance[3]	common		common
macular oedema	not known		not known

Adverse reaction	Frequency of adverse reactions		
	Pioglitazone	**Metformin**	**Glubrava**
Gastrointestinal disorders[4]			
abdominal pain		very common	very common
diarrhoea		very common	very common
flatulence			uncommon
loss of appetite		very common	very common
nausea		very common	very common
vomiting		very common	very common
Hepatobiliary disorders			
hepatitis[5]		not known	not known
Skin and subcutaneous tissue disorders			
erythema		very rare	very rare
pruritis		very rare	very rare
urticaria		very rare	very rare
Musculoskeletal and connective tissue disorders			
bone fracture[6]	common		common
arthralgia			common
Renal and urinary disorders			
haematuria			common
Reproductive system and breast disorders			
erectile dysfunction			common
General disorders and administration site conditions			
oedema[7]			common
Investigations			
weight increased[8]	common		common
alanine aminotransferase increased[9]	not known		not known
liver function tests abnormal[5]		not known	not known

Description of selected adverse reactions

[1] Postmarketing reports of hypersensitivity reactions in patients treated with pioglitazone have been reported. These reactions include anaphylaxis, angioedema, and urticaria.

[2] Long term treatment of metformin has been associated with a decrease of vitamin B12 absorption with decrease of serum levels. Consideration of such aetiology is recommended if a patient presents with megaloplastic anaemia.

[3] Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens.

[4] Gastrointestinal disorders occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[5] Isolated reports: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

[6] A pooled analysis was conducted of adverse event reports of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8,100 patients in the pioglitazone-treated groups and 7,400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of

fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).
In the 3.5 year PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. The observed excess risk of fractures for women on pioglitazone in this study is therefore 0.5 fractures per 100 patient years of use. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). Post-marketing, bone fractures have been reported in both male and female patients (see section 4.4).

[7] In active comparator controlled trials oedema was reported in 6.3% of patients treated with metformin and pioglitazone, whereas the addition of sulphonylurea to metformin treatment resulted in oedema in 2.2% of patients. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

[8] In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2-3 kg over one year. In combination trials pioglitazone added to metformin resulted in mean weight increase over one year of 1.5 kg.

[9] In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included insulin. However, this did not lead to an increase in mortality in this study. In this study in patients receiving pioglitazone and insulin, a higher percentage of patients with heart failure was observed in patients aged ≥ 65 years compared with those less than 65 years (9.7% compared to 4.0%). In patients on insulin with no pioglitazone the incidence of heart failure was 8.2% in those ≥ 65 years compared to 4.0% in patients less than 65 years. Heart failure has been reported with marketing use of pioglitazone and more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

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.

The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD05.

Glubrava combines two antihyperglycaemic active substances with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes mellitus: pioglitazone, a member of the thiazolidinedione class and metformin hydrochloride, a member of the biguanide class. Thiazolidinediones act primarily by reducing insulin resistance and biguanides act primarily by decreasing endogenous hepatic glucose production.

Pioglitazone and metformin combination

The fixed dose combination tablet of pioglitazone 15 mg/metformin 850 mg BID (N=201), pioglitazone 15 mg BID (N=189), and metformin 850 mg BID (N=210) were evaluated in type 2 diabetes mellitus patients with mean baseline HbA_{1c} of 9.5% in a randomised double-blind, parallel-group study. Previous anti-diabetic medicinal products were discontinued for 12 weeks prior to baseline measurements. After 24 weeks of treatment, the primary endpoint of mean change from baseline in HbA_{1c} was -1.83% in the combination group versus -0.96% in the pioglitazone group ($p< 0.0001$) and -0.99% in the metformin group ($p< 0.0001$).

The safety profile seen in this study reflected the known adverse reactions seen with the individual products and did not suggest any new safety issues.

Pioglitazone

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.

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 $HbA_{1c} \geq 8.0\%$ 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 $HbA_{1c} < 8.0\%$) 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 HbA_{1c} was similar between treatment groups after one year. The rate of deterioration of HbA_{1c} 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 HbA_{1c} 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 where observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced postprandial 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, 5,238 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 sulphonylurea. 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, acetylsalicylic acid, 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 incidence of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes mellitus. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Glubrava 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

Glubrava

Bioequivalence studies in healthy volunteers have shown Glubrava to be bioequivalent to the administration of pioglitazone and metformin given as separate tablets.

Food had no effect on the AUC and C_{max} of pioglitazone when Glubrava was administered to healthy volunteers. However, in the case of metformin, in the fed state the mean AUC and C_{max} were lower (13% and 28% respectively). T_{max} was delayed by food by approximately 1.9 h for pioglitazone and 0.8 h for metformin.

The following statements reflect the pharmacokinetic properties of the individual active substances of Glubrava.

Pioglitazone

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.

Linearity/non-linearity
Single dose studies demonstrate linearity of pharmacokinetics in the therapeutic dose range.

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.

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.

Linearity/non-linearity
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

5.3 Preclinical safety data

No animal studies have been conducted with the combined products of Glubrava. The following data are findings in studies performed with pioglitazone or metformin individually.

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.

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 tumourigenic 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.

Metformin

Non-clinical 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

Tablet core
Microcrystalline cellulose
Povidone (K30)
Croscarmellose sodium
Magnesium stearate

Film coat
Hypromellose
Macrogol 8000
Talc
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blisters.
Packs of 14, 28, 30, 50, 56, 60, 90, 98 and 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/421/001
EU/1/07/421/002
EU/1/07/421/003
EU/1/07/421/004
EU/1/07/421/005
EU/1/07/421/006
EU/1/07/421/007

EU/1/07/421/008
EU/1/07/421/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 December 2007
Date of latest renewal: 10 November 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Delpharm Novara S.r.l.
Via Crosa, 86
28065 Cerano (NO)
Italy

Takeda Ireland Limited
Bray Business Park
Kilruddery
County Wicklow
Ireland

Lilly S.A.
Avda. de la Industria 30
28108 Alcobendas
Madrid
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Glubrava 15 mg/850 mg film-coated tablets

pioglitazone/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg pioglitazone (as hydrochloride) and 850 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet.
14 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
90 tablets
98 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/421/001 14 tablets
EU/1/07/421/002 28 tablets
EU/1/07/421/003 30 tablets
EU/1/07/421/004 50 tablets
EU/1/07/421/005 56 tablets
EU/1/07/421/006 60 tablets
EU/1/07/421/007 90 tablets
EU/1/07/421/008 98 tablets
EU/1/07/421/009 180 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Glubrava 15 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Glubrava 15 mg/850 mg tablets

pioglitazone/metformin hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

FOR CALENDARISED PACKS:

Mon. 1	Mon. 2
Tue. 1	Tue. 2
Wed. 1	Wed. 2
Thu. 1	Thu. 2
Fri. 1	Fri. 2
Sat. 1	Sat. 2
Sun. 1	Sun. 2

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Glubrava 15 mg/850 mg film-coated tablets
pioglitazone/metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Glubrava is and what it is used for

Glubrava contains pioglitazone and metformin which are anti-diabetic medicines, used to control blood sugar level.

It is used in adults to treat type 2 (non-insulin dependent) diabetes mellitus when treatment with metformin alone is not sufficient. This type 2 diabetes usually develops in adulthood particularly as a result of the person being overweight and where the body either does not produce enough insulin (a hormone that controls blood sugar levels), or cannot effectively use the insulin it produces.

Glubrava helps control the level of sugar in your blood when you have type 2 diabetes by helping your body make better use of the insulin it produces. If 3 to 6 months after starting Glubrava your sugar control is not improved, the medicine should be discontinued.

2. What you need to know before you take Glubrava

Do not take Glubrava
- if you are allergic to pioglitazone, metformin or any of the other ingredients of this medicine (listed in section 6).
- if you have heart failure or have had heart failure in the past.
- if you recently had a heart attack, have severe circulatory problems including shock, or breathing difficulties.
- if you have liver disease.
- if you drink alcohol excessively (either every day or only from time to time).
- if you have uncontrolled diabetes with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see section “Risk of lactic acidosis”) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- if you have or have ever had bladder cancer.
- if you have blood in your urine that your doctor has not checked.

- if you have severely reduced kidney function.
- if you have a severe infection or are dehydrated.
- if you are going to have a certain type of X-ray with an injectable dye, talk to your doctor as you must stop taking Glubrava for a certain period of time before and after the examination.
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor or pharmacist before taking Glubrava (also see section 4)
- if you have a problem with your heart. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin together experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).
- if you retain water (fluid retention) or have heart failure problems in particular if you are over 75 years old. If you take anti-inflammatory medicines which can also cause fluid retention and swelling, you must also tell your doctor.
- if you have a special type of diabetic eye disease called macular oedema (swelling of the back of the eye), talk to your doctor if you notice any change to your vision.
- if you have cysts on your ovaries (polycystic ovary syndrome). There may be an increased possibility of becoming pregnant because you may ovulate again when you take Glubrava. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- if you have a problem with your liver. Before you start taking Glubrava you will have a blood sample taken to check your liver function. This check should be repeated at intervals. Inform your doctor as soon as possible if you develop symptoms suggesting a problem with your liver (like feeling sick without explanations, vomiting, stomach ache, tiredness, loss of appetite and/or dark urine) as your liver function should be checked.

You may also experience a reduction in blood count (anaemia).
Your doctor may take blood tests to monitor your blood cell levels and liver function.

Risk of lactic acidosis
Glubrava may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).
If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Glubrava for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking Glubrava and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

During treatment with Glubrava, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

If you need to have major surgery you must stop taking Glubrava during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Glubrava.

Hypoglycaemia
If you take Glubrava with other medicines for diabetes, it is more likely that your blood sugar could fall below the normal level (hypoglycaemia). If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast heart-beating, vision disorders or difficulty in concentration, you should take some sugar to increase your blood sugar level again. Ask your doctor or pharmacist for more information if you are not sure how to recognise this. It is recommended that you carry some sugar lumps, sweets, biscuits or sugary fruit juice.
The level of sugar in your blood or urine should be checked regularly.

Broken bones
A higher number of bone fractures was seen in patients, particularly women taking pioglitazone. Your doctor will take this into account when treating your diabetes.

Children and adolescents
Use in children and adolescents under 18 years is not recommended.

Other medicines and Glubrava
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Glubrava before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Glubrava.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dose of Glubrava. This is because some medicines can weaken or strenghten the effect of Glubrava on the level of sugar in your blood.

The following medicines can increase the blood sugar lowering effect of Glubrava. This can lead to a risk of hypoglycaemia (low blood sugar):
- gemfibrozil (to lower high cholesterol level)
- angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (to treat high blood pressure)
- cimetidine (to reduce stomach acid)

The following medicines may decrease the blood sugar lowering effect of Glubrava. This can lead to a risk of hyperglycaemia (high blood sugar level):
- rifampicin (to treat tuberculosis and other infections)
- glucocorticoids (to treat allergies and inflammation)
- beta-2-agonists (to treat asthma)
- medicines which increase urine production (diuretics, to treat high blood pressure)

Other:
Medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib).

Glubrava with alcohol
Avoid excessive alcohol intake while taking Glubrava since this may increase the risk of lactic acidosis (see section “Risk of lactic acidosis”).

Pregnancy and breast-feeding
- you must tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. You should not use this medicine if you are pregnant. If you wish to become pregnant, your doctor will advise you to discontinue this medicine.

- do not use this medicine if you are breastfeeding or are planning to breast-feed (see section "Do not take Glubrava").

Driving and using machines
This medicine will not affect your ability to drive or use machines but take care if you experience abnormal vision.

Glubrava contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Glubrava

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet taken twice daily. If necessary your doctor may tell you to take a different dose. If you have reduced kidney function, your doctor may prescribe a lower dose, which may need to be given as separate tablets of pioglitazone and metformin.
You should swallow the tablets with a glass of water. You may take your tablets with or just after food to reduce the chance of an upset stomach.

If you are following a special diet for diabetes, you should continue with this while you are taking Glubrava.

Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

Your doctor will ask you to have blood tests periodically during treatment with Glubrava. This is to check that your liver is working normally. At least once a year (more often if you are elderly or have kidney problems) your doctor will check that your kidneys are working normally.

If you take more Glubrava than you should
If you accidentally take too many tablets, or if someone else or a child takes your medicine, talk to a doctor or pharmacist immediately. Your blood sugar could fall below the normal level and can be increased by taking sugar. It is recommended that you carry some sugar lumps, sweets, biscuits or sugary fruit juice.

If you forget to take Glubrava
Take Glubrava daily as prescribed. However if you miss a dose, skip the missed dose and just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Glubrava
Glubrava should be used every day to work properly. If you stop using Glubrava, your blood sugar may go up. Talk to your doctor before stopping this treatment.

If you have any further questions on the use of this medicine ask your doctor or pharmacist.

4. Possible side effects

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

In particular, patients have experienced the following serious side effects:

Glubrava may cause a very rare (may affect up to 1 in 10,000), but very serious side effect called lactic acidosis (see section "Warnings and precautions"). If this happens you must **stop taking Glubrava and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

Bladder cancer has been experienced uncommonly (may affect up to 1 in 100 people) in patients taking Glubrava. Signs and symptoms include blood in your urine, pain when urinating or a sudden need to urinate. If you experience any of these, talk to your doctor as soon as possible.

Localised swelling (oedema) has also been experienced commonly (may affect up to 1 in 10 people) in patients taking Glubrava in combination with insulin. If you experience this side effect, talk to your doctor as soon as possible.

Broken bones have been reported commonly (may affect up to 1 in 10 people) in female patients taking Glubrava and have also been reported in male patients (frequency cannot be estimated from the available data) taking Glubrava. If you experience this side effect, talk to your doctor as soon as possible.

Blurred vision due to swelling (or fluid) at the back of the eye (macular oedema) has also been reported in patients taking Glubrava (frequency cannot be estimated from the available data). If you experience this symptom for the first time, talk to your doctor as soon as possible. Also, if you already have blurred vision and the symptom gets worse, talk to your doctor as soon as possible.

Allergic reactions have been reported with frequency not known (cannot be estimated from the available data) in patients taking Glubrava. If you have a serious allergic reaction, including hives and swelling of the face, lips, tongue, or throat that may cause difficulty in breathing or swallowing stop taking this medicine and talk to your doctor immediately.

The following side effects have been experienced by some patients taking Glubrava

Very common (may affect more than 1 in 10 people)
- stomach ache
- feeling sick (nausea)
- vomiting
- diarrhoea
- loss of appetite

Common
- weight gain
- headache
- respiratory infection
- abnormal vision
- joint pain
- impotence
- blood in urine
- reduction in blood count (anaemia)
- numbness
- taste disturbance

Uncommon
- inflammation of the sinuses (sinusitis)
- gas
- difficulty sleeping (insomnia)

Very rare
- decrease in amount of vitamin B_{12} in the blood
- redness of the skin
- itchy skin
- raised and itchy rash (hives)

Not known
- inflammation of the liver (hepatitis)
- liver does not work as well as it should (changes in liver enzymes)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Glubrava

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Glubrava contains
- The active substances are pioglitazone and metformin hydrochloride. Each tablet contains 15 mg of pioglitazone (as hydrochloride) and 850 mg of metformin hydrochloride.
- The other ingredients are microcrystalline cellulose, povidone (K30), croscarmellose sodium magnesium stearate, hypromellose, macrogol 8000, talc and titanium dioxide (E171).

What Glubrava looks like and contents of the pack
The film-coated tablets (tablets) are white to off white, oblong, convex, embossed '15 / 850' on one face and '4833M' on the other. They are supplied in aluminium/aluminium blister in packs of 14, 28, 30, 50, 56, 60, 90, 98 or 180 tablets.

Not all pack sizes may be marketed.

Marketing authorisation holder:
Takeda Pharma A/S,
Delta Park 45
2665 Vallensbaek Strand
Denmark

Manufacturer:
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Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.