ינואר 2014

רופא/ה, רוקח/ת נכבד/ה
חברת טבע שמחה לבשר על רישום התכשיר החדש הבא:

Competact 15/850 mg
Film Coated Tablets

קומפטקט 850/15 מ"ג
טבליות מצופות

Each tablet contains:
Pioglitazone (as HCl) 15 mg
Metformin Hdrochloride 850 mg

תכשיר חדש

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

Competact 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 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.

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"This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved." Date of approval: November 2013

SUMMARY OF PRODUCT CHARACTERSITICS

1. NAME OF THE MEDICINAL PRODUCT

Competact 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 a 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

Competact 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 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 (see section 4.4).

4.2 Posology and method of administration

Posology

The usual dose of Competact is 30 mg/day pioglitazone plus 1700 mg/day of metformin hydrochloride (this dose is achievable with one tablet of Competact 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 Competact.

When clinically appropriate, direct change from metformin monotherapy to Competact 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 Competact 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

Competact should not be used in patients with renal failure or renal dysfunction (creatinine clearance< 60 ml/min)(see sections 4.3 and 4.4).

Hepatic impairment

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

Paediatric population

The safety and efficacy of Competact 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 Competact with, or just after food, may reduce gastrointestinal symptoms associated with metformin.

4.3 Contraindications

Competact is contraindicated in patients with:
- Hypersensitivity to the active substances or to any of the excipients
- Cardiac failure or history of cardiac failure (NYHA stages I to IV)
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory
- failure, recent myocardial infarction, shock
- Hepatic impairment
- Acute alcohol intoxication, alcoholism
- Diabetic ketoacidosis or diabetic pre-coma
- Renal failure or renal dysfunction (creatinine clearance <60 ml/min) (see section 4.4).
- 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

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 is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function

As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limits of normal and in elderly subjects

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 Competact 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. Competact 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 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. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.

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 Competact undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Competact in all patients. Therapy with Competact 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 Competact, 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 Competact 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 Competact 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 Competact contains metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, Competact should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 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 in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

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.

In the 3.5 year cardiovascular risk 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. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). The observed excess risk of fractures for women on pioglitazone in this study is therefore 0.5 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 women treated with pioglitazone.

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).

4.5 Interaction with other medicinal products and other forms of interaction

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

Intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of Competact (see section 4.4). Avoid consumption of alcohol and medicinal products containing alcohol.

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.

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 dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage 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.

4.6 Fertility, pregnancy and lactation

For Competact no preclinical or clinical data on exposed pregnancies or lactation are available.

Women of childbearing potential / Contraception in males and females

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

Pregnancy

Risk related to pioglitazone

There are no adequate human data from the use of pioglitazone in pregnant women. Animal studies have not shown teratogenic effects but have shown foetotoxicity related to the pharmacologic action (see section 5.3).

Risk related to metformin

Animal studies have not revealed teratogenic effects. Small clinical trials have not revealed metformin to have malformative effects.

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

Breast-feeding

Both pioglitazone and metformin have been shown to be present in the milk of lactating rats. It is not known whether breast-feeding will lead to exposure of the infant to the medicinal product. Competact must therefore not be used in women who are 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

Competact has no or negligible effect 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 Competact tablets and co-administered pioglitazone and metformin (see section 5.1). Bioequivalence of Competact with co-administered pioglitazone and metformin has also been demonstrated (see section 5.2). 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 in less than 1 case per 10,000 patients (see section 4.4) and other reactions such as bone fracture, weight increase and oedema may occur in less than 1 case per 10 patients (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 frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

Adverse reaction	**Frequency of adverse reactions**		
	Pioglitazone	**Metformin**	**Competact**
Infections and infestations			
upper respiratory tract infection	common		common
sinusitis	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
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
bladder cancer	uncommon		uncommon
Eye disorders			
visual disturbance[3]	common		common
macular oedema	not known		not known

Adverse reaction	Frequency of adverse reactions		
	Pioglitazone	**Metformin**	**Competact**
Gastrointestinal disorders[4]			
abdominal pain		very common	very common
diarrhea		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 reactions of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 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%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

[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 rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

4.9 Overdose

No data are available with regard to overdose of Competact.

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.

Competact combines two antihyperglycaemic active substances with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: 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 HbA1C of 9.5% in a randomised double-blind, parallel-group study. Previous anti-diabetic medication was discontinued for 12 weeks prior to baseline measurements. After 24 weeks of treatment, the primary endpoint of mean change from baseline in HbA1c 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, 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 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, 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 incidence of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

<u>Metformin</u>

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. 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 Competact 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

Competact

Bioequivalence studies in healthy volunteers have shown Competact 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 Competact 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 Competact.

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.

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.

5.3 Preclinical safety data

No animal studies have been conducted with the combined products in Competact. 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 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.

Metformin

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

Environmental Risk Assessment: no environmental impact is anticipated from the clinical use of pioglitazone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Povidone
Croscarmellose sodium
Magnesium stearate

Film coat
Hypromellose
Macrogol 8000
Talc
Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store in a dry place below 25°C.

6.4 Nature and contents of container

Aluminium/aluminium blisters, packs of 14, 28, 30, 50, 56, 60, 90, 98, 112, 180, 196 (2 x 98) tablets or 60 x 1 tablets in aluminium/aluminium perforated unit dose blisters.

6.5 Special precautions for disposal

No special requirements.

7 REGISTRATION NUMBER

150 65 33826 00.

8 MANUFACTURER

Takeda Global Research and Development Centre (Europe) Ltd
London,
United Kingdom

9 LICENCE HOLDER

Abic Marketing Ltd.,
P.O.Box 8077,
Netanya.

__עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו – 1986__

התרופה משווקת עם מרשם רופא בלבד.

קומפטקט 15 מ"ג/850 מ"ג

טבליות מצופות פילם

הרכב חומרים פעילים

כל טבליה מכילה:

פיוגליטאזון (הידרוכלוריד) 15 מ"ג	Pioglitazone (as HCl) 15 mg
מטפורמין הידרוכלוריד 850 מ"ג	Metformin HCl 850 mg

לרשימת החומרים הבלתי פעילים בתכשיר ראה סעיף 6 - "מידע נוסף".

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.

תרופה זו נרשמה לטיפול במחלתך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מצבם הרפואי דומה.

השימוש בתרופה זו אינו מומלץ בילדים מתחת לגיל 18 שנים.

1. למה מיועדת התרופה?

התרופה מיועדת לטיפול בסוכרת מסוג 2 (ללא תלות באינסולין) במבוגרים שרמת הסוכר שלהם בדם לא ניתנת לאיזון בטיפול עם מטפורמין לבדו.

סוכרת מסוג 2 בדרך כלל מתפתחת בבגרות במיוחד אצל אנשים בעלי עודף משקל ובמקרים בהם הגוף אינו מייצר מספיק אינסולין (הורמון האחראי לאיזון רמת הסוכר בדם) או כאשר פעולת האינסולין בגוף לקויה.

קומפטקט עוזר לאזן את רמת הסוכר בדם על ידי שיפור תגובת תאי הגוף לאינסולין המיוצר בגוף.

קבוצה תרפויטית:

פיוגליטאזון: שייך לקבוצת התיאזולידינדיונים.

מטפורמין: שייך לקבוצת הביגואנידים.

2. לפני השימוש בתרופה

☒ **אין להשתמש בתכשיר אם:**
- אין להשתמש בתרופה זו אם ידועה רגישות לפיוגליטאזון, מטפורמין או לאחד ממרכיבי קומפטקט.
- אין להשתמש אם הינך סובל או סבלת בעבר מאי ספיקת לב.
- אין להשתמש בתרופה זו אם סבלת לאחרונה מהתקף לב, מבעיות חמורות במחזור הדם או קשיי נשימה.
- אין להשתמש בתרופה זו אם הינך סובל ממחלת כבד.
- אין להשתמש בתרופה במידה והינך צורך אלכוהול בצורה מוגזמת (שתייה יומיומית או שתייה מעת לעת).
- אין להשתמש בתרופה זו אם הינך סובל מחמצת סוכרתית (קטואצידוזיס), סיבוך של סוכרת הגורם לאיבוד משקל מהיר, בחילה או הקאה.
- אין להשתמש אם הינך סובל או סבלת בעבר מסרטן של שלפוחית השתן.
- אין להשתמש בתרופה במידה ויש לך דם בשתן שהרופא לא איבחן.
- אין להשתמש בתרופה במידה והינך סובל מבעיה בכליות.
- אין להשתמש בתרופה במקרה של דלקת חמורה או התייבשות.
- אין להשתמש בתרופה אם הינך צריך לעבור צילום רנטגן (X-ray) הכולל הזרקת חומר צבע - במקרה זה יש צורך להפסיק נטילת קומפטקט לפני הבדיקה ולמשך מספר ימים לאחר הבדיקה.
- אין ליטול תרופה זו אם הינך מניקה.

אזהרות מיוחדות הנוגעות בשימוש בתרופה

! יש לדווח לרופא לפני התחלת הטיפול אם:
- אם הינך סובל מבעיה בלב. באנשים מסוימים הסובלים מסוכרת מסוג 2 לאורך שנים רבות וממחלות לבביות או משבץ מוחי אשר נטלו פיוגליטאזון בשילוב אינסולין, התפתחה אי ספיקת לב. יש לדווח לרופא בהקדם האפשרי במידה והינך חש בסימנים לאי ספיקת לב כגון קוצר נשימה בלתי רגיל או עליה חדה במשקל הגוף או בצקת מקומית (נפיחות).
- אם הינך סובל מאצירת נוזלים או אם הינך סובל מאי ספיקת לב, במיוחד במטופלים מעל גיל 75 שנה.

  במידה והינך נוטל תרופות נוגדות דלקות העלולות גם לגרום לאצירת נוזלים ולנפיחות, עליך גם להיוועץ ברופא.
- אם הינך סובל ממחלת עיניים האופיינית לסוכרתיים, הנקראת Macular oedema (נפיחות בחלק האחורי של העין).
- אם הינך עומד לעבור ניתוח תחת הרדמה כללית - יש צורך להפסיק הטיפול עם קומפטקט למשך מספר ימים לפני הניתוח ולאחריו.
- אם הינך סובלת מתסמונת שחלות פוליציסטיות. קומפטקט עלול לגרום לביוץ ולהעלות את הסיכוי להיכנס להריון. על מנת להימנע מהריון בלתי מתוכנן, מומלץ להשתמש בתכשירים למניעת הריון.
- אם הינך סובל מבעיה בכבד. לפני התחלת הטיפול עם קומפטקט ובמהלכו יש לערוך בדיקות דם לבדיקת תפקודי הכבד. אם הינך חש בסמפטומים המרמזים על בעיה בכבד (כגון הרגשה של חולי ללא הסבר, הקאות, כאב בטן, עייפות, ירידה בתיאבון ו/או שתן כהה), יש לפנות לרופא מיד להערכת מצבך.
- במידה והינך נוטל תרופות נוספות לסוכרת, יש לנקוט באמצעי זהירות למניעת התפתחות מצב של תת רמות סוכר בדם (היפוגליקמיה).
- יש לערוך בדיקות דם בתדירות שתיקבע על ידי הרופא המטפל מאחר ועלולה להיות ירידה בספירת הדם (אנמיה).
- בחולים המטופלים בפיוגליטאזון, במיוחד בנשים, נצפה מספר גבוה של שברים בעצמות. יש להתייעץ עם הרופא.
- הרופא המטפל יערוך בדיקות להערכת יעילות הטיפול עם קומפטקט 3 עד 6 חודשים לאחר התחלת הטיפול.

! אם אתה לוקח או אם לקחת לאחרונה תרופות אחרות כולל תרופות ללא מרשם רופא ותוספי תזונה, ספר על כך לרופא או לרוקח.

במיוחד יש לדווח לרופא במידה והינך נוטל את התרופות הבאות:
- גמפיברוזיל (להורדת כולסטרול)
- ריפאמפיצין (לטיפול בשחפת ודלקות נוספות)
- סימטידין (לאולקוס)
- גלוקוקורטיקואידים (לטיפול בדלקות)
- ביתא-2-אגוניסט (לטיפול באסטמה)
- משתנים (להורדת רמות נוזלים עודפים בגוף)
- מעכבי ACE (ליתר לחץ דם)

במידה והינך נוטל אחת מהתרופות הללו, יש לבדוק את רמת הסוכר בדם, על מנת להעריך את המינון המתאים של קומפטקט.

! שימוש יחד עם אוכל ושתיה

מומלץ ליטול התרופה עם או מיד אחרי ארוחה (להפחתת הסיכון לכאב בטן).

יש להימנע משתיית אלכוהול או נטילת תרופות המכילות אלכוהול, מאחר ואלכוהול עלול להעלות את הסיכון של חמצת לקטית (ראה סעיף 4 "תופעות לוואי").

! הריון והנקה

אין להשתמש בתרופה זו אם הינך בהריון או מתכננת הריון.

אין להשתמש בתרופה זו אם הינך מניקה או מתכננת להניק.

! שימוש בילדים

תרופה זו אינה מומלצת לשימוש בילדים מתחת לגיל 18 שנים.

! נהיגה ושימוש במכונות

התרופה אינה פוגמת בכושר הנהיגה או ביכולת להפעיל מכונות, אך יש להיזהר במידה והינך חש בליקויים בראיה בזמן הטיפול.

3. כיצד תשתמש בתרופה?

תמיד יש להשתמש בתרופה לפי הוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח.

המינון לפי הוראות הרופא בלבד.

יש להשתמש בתרופה זו בזמנים קצובים כפי שנקבע על ידי הרופא המטפל.

מינון:

המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.

אופן השימוש המקובל בדרך כלל הוא כדלקמן:

יש ליטול טבליה אחת של קומפטקט פעמיים ביום. במידת הצורך הרופא יחליט על מינון שונה.

אין לעבור על המנה המומלצת.

יש לבלוע הטבליות עם כוס מים. מומלץ ליטול הטבליה עם מזון.

במידה והינך נמצא תחת דיאטה מיוחדת לסוכרתיים, יש להתמיד בה לאורך נטילת קומפטקט.

בדיקות ומעקב
- יש לעקוב אחר משקל גופך בתדירות קבועה. במידה וישנה עליה במשקל הגוף יש להיוועץ ברופא.
- יש לערוך בדיקות דם תקופתיות בזמן השימוש עם קומפטקט על מנת לעקוב אחר תקינות תפקודי הכבד.
- בתקופת הטיפול יש לערוך בדיקות תפקודי כליה לפחות פעם בשנה (אם הינך קשיש או סובל מבעיות כליה יש לערוך את הבדיקה לעיתים קרובות יותר).

אם נטלת מנת יתר או אם בטעות בלע ילד מן התרופה, יש לפנות מיד לרופא או לחדר מיון של בית חולים ולהביא את אריזת התרופה איתך.

תופעות של מינון יתר:

במקרה זה רמות הסוכר בדם עלולות לרדת יתר על המידה. ניתן להעלות את רמת הסוכר בדם על ידי אכילת מזון עשיר בסוכר. מומלץ למטופל לשאת עימו מזון המכיל סוכר (כגון: סוכריות, ממתקים, עוגיות או מיץ ממותק).

אם שכחת ליטול את התרופה בזמן הדרוש, קח את המנה הבאה בזמן הרגיל. אין ליטול שתי מנות יחד כדי לפצות על המנה שנשכחה.

יש להתמיד בטיפול כפי שהומלץ על ידי הרופא, גם אם חל שיפור במצב בריאותך, אין להפסיק הטיפול ללא התייעצות עם הרופא או הרוקח.

4. תופעות לוואי

כמו לכל תרופה, השימוש בקומפטקט עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן.
- באופן נדיר מאוד במטופלים הנוטלים מטפורמין (אחד המרכיבים של קומפטקט) יכול להתפתח מצב של חמצת לקטית (עודף של חומצה לקטית בדם) במיוחד במטופלים עם תפקודי כליה ליקויים. הסמפטומים כוללים הרגשת קור וחוסר נוחות, בחילה והקאות חמורות, כאב בטן, ירידה במשקל בלתי מוסברת או נשימה מהירה. **אם הינך חש באחת מתופעות אלו, יש להפסיק את נטילת קומפטקט ולפנות לרופא מיד.**
- סרטן שלפוחית השתן עלול להתרחש באופן לא שכיח (תדירות של 1 עד 10 מתוך 1,000 מטופלים) במטופלים הנוטלים קומפטקט. סימנים וסמפטומים כוללים דם בשתן, כאב במתן שתן או דחיפות פתאומית במתן שתן. אם הינך חש באחת מתופעות אלו, יש להיוועץ ברופא בהקדם האפשרי.
- ראיה מטושטשת עקב נפיחות (או נוזלים) בחלק האחורי של העין דווחה בשכיחות שאינה ידועה. אם הינך חש בתופעה זו לראשונה יש להיוועץ ברופא בהקדם האפשרי. במידה והינך סובל מראיה מטושטשת וחלה החמרה בסמפטומים יש לפנות לרופא בהקדם האפשרי.
- בקרב מטופלים שנטלו קומפטקט, דווחו מקרים (תדירות אינה ידועה) של תגובות אלרגיות. במידה והינך חש תגובה אלרגית חמורה, כולל חרלת (גירוד) ונפיחות בפנים, בשפתיים, בלשון או בגרון העלולה לגרום לקשיי נשימה או בליעה, עליך להפסיק את התרופה ולהיוועץ ברופא בהקדם.

תופעות לוואי נוספות

תופעות לוואי שכיחות מאוד (משפיע על יותר מ– 1 עד 10 מטופלים):
- כאב בטן
- בחילה
- הקאות
- שלשול
- ירידה בתאבון

תופעות לוואי שכיחות (משפיע על 1 עד 10 מתוך 100 מטופלים):
- נפיחות מקומית (בצקת)
- עליה במשקל
- כאב ראש
- דלקות של מערכת הנשימה
- ליקויים בראיה
- כאב מפרקים
- אין אונות (אימפוטנציה)
- דם בשתן
- ירידה בספירת תאי הדם (אנמיה)
- חוסר תחושה (תחושת נימול)
- הפרעות בחוש טעם
- שברים בעצמות

תופעות לוואי לא שכיחות (משפיע על 1 עד 10 מתוך 1,000 מטופלים):
- דלקת של הסינוסים (סינוסיטיס)
- נפיחות (גזים)
- נדודי שינה

תופעות לוואי מאוד נדירות (משפיע על פחות מ– 1 מתוך 10,000 מטופלים):
- ירידה ברמת ויטמין B_{12} בדם
- חמצת לקטית (עודף חומצה לקטית בדם)
- אדמומיות בעור
- גירוד בעור
- פריחה הכוללת נגעים אדומים, בולטים ומגרדים (סרפדת)

תופעות לוואי בעלות שכיחות לא ידועה (לא ניתן לקבוע תדירות לפי הנתונים הקיימים):
- ראיה מטושטשת עקב נפיחות (או נוזלים) בחלק האחורי של העין
- דלקת של הכבד (הפטיטיס)
- לקויים בתפקוד הכבד (שינויים ברמות אנזימי הכבד)
- תגובות אלרגיות

אם אחת מתופעות הלוואי מחמירה, או אם אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא.

5. איך לאחסן את התרופה?

מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.

אין ליטול תרופות בחושך! בדוק התווית והמנה __בכל פעם__ שהינך נוטל תרופה. הרכב משקפיים אם הינך זקוק להם.

אין להשתמש בתרופה אחרי תאריך התפוגה (Expiry date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.

יש לאחסן במקום יבש, מתחת ל- 25ºC.

6. מידע נוסף

נוסף על החומר הפעיל התרופה מכילה גם:

Microcrystalline cellulose, Povidone, Croscarmellose sodium, Magnesium stearate, Hypromellose, Macrogol 8000, Talc, Titanium dioxide.

כל טבליה של קומפטקט מכילה: 3.3-5 מ"ג נתרן.

כיצד נראית התרופה ומה תוכן האריזה

האריזה מכילה 56 טבליות.

צורת הטבליה: טבליה קמורה ומאורכת בצבע לבן, בצידה האחד מופיע המספר '15/850' ובצידה השני מופיע '4833M'.

בעל הרישום

אביק שיווק בע"מ, ת"ד 8077, נתניה 42504.

שם היצרן וכתובתו

Takeda Pharma A/S, Denmark.

עלון זה נבדק ואושר ע"י משרד הבריאות בתאריך: נובמבר 2013.

מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות: 150.65.33826.00

לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.

COMP CTAB PL SH 120114

__نشرة للمستهلك بموجب أنظمة الصيدلة (مستحضرات) ـ ١٩٨٦__

يسوق الدواء حسب وصفة طبيب فقط.

كومبيتاكت ١٥ ملغ/ ٨٥٠ ملغ

أقراص مطلية بفلم

تركيب المواد الفعالة

يحتوي كل قرص على:

بيوچليتازون (هيدروكلوريد) ١٥ ملغ	Pioglitazone (as HCl) 15 mg
ميتفورمين هيدروكلوريد ٨٥٠ ملغ	Metformin HCl 850 mg

لقائمة المواد غير الفعالة في المستحضر أنظر الفقرة ٦ ـ «معلومات إضافية».

إقرأ النشرة بتمعن حتى نهايتها قبل إستعمالك للدواء. تحتوي هذه النشرة على معلومات موجزة عن الدواء. إذا توفرت لديك أسئلة إضافية، راجع الطبيب أو الصيدلي.

وصف هذا الدواء لعلاج مرضك. لا تعطيه للآخرين. فهو قد يضرهم حتى ولو بدا لك أن حالتهم الطبية مشابهة لحالتك.

لا يوصى بإستعمال هذا الدواء للأطفال دون عمر ١٨ سنة.

١) لأي غرض مخصص الدواء؟

الدواء مخصص لعلاج السكري من نوع ٢ (غير متعلق بالإينسولين) لدى بالغين لا يمكن موازنة مستوى السكر في الدم لديهم من خلال العلاجٍ بـ ميتفورمين لوحده.

يتطور السكري من نوع ٢ عادة في سن البلوغ خاصة لدى أشخاص ذوي وزن زائد وفي حالات لا ينتج فيها الجسم ما يكفي من الإينسولين (هورمون مسؤول لتوازن نسبة السكر في الدم) أو إذا وُجد خلل في عمل الاينسولين في الجسم.

يساعد كومبيتاكت في موازنة مستوى السكر في الدم من خلال تحسين إستجابة خلايا الجسم للإينسولين الذي يُنتج في الجسم.

الفصيلة العلاجية:

بيوچليتازون: ينتمي إلى فصيلة تيازوليدينديون.

ميتفورمين: ينتمي لفصيلة بيچوانيدات.

٢) قبل إستعمال الدواء

☒ **لا يجوز إستعمال المستحضر إذا :**
- لا يجوز إستعمال هذا الدواء إذا وجدت حساسية لبيوچليتازون، ميتفورمين أو لأحد مركبات كومبيتاكت.
- لا يجوز الإستعمال إذا كنت تعاني أو عانيت فيٍ الماضي من قصور قلب.
- لا يجوز إستعمال هذا الدواء إذا عانيت مؤخراً من نوبة قلبية، من مشاكل خطيرة في الدورة الدموية أو صعوبات تنفسية.
- لا يجوز إستعمال هذا الدواء إذا كنت تعاني من مرض كبدي.
- لا يجوز إستعمال الدواء إذا كنت تفرط بشرب الكحول (شرب يومي أو شرب من حين لآخر).
- لا يجوز إستعمال هذا الدواء إذا كنت تعاني من حماض سكري (ketoacidosis)، إختلاط للسكري الذي يسبب فقدان وزن سريع، غثيان أو تقيؤ.
- لا يجوز الإستعمال إذا كنت تعاني أو عانيت في الماضي من سرطان المثانة.
- لا يجوز إستعمال الدواء في حال لديك دم في البول لم يشخصه الطبيب.
- لا يجوز إستعمال الدواء إذا كنت تعاني من مشكلة في الكلى.
- لا يجوز إستعمال الدواء في حال وجود إلتهاب شديد أو تجفاف.
- لا يجوز إستعمال الدواء إذا كنت بحاجة لإجراء تصوير رنتچن (X- ray) حيث يشمل حقن مادة ملونة ـ في هذه الحالة يجب التوقف عن تناول كومبيتاكت قبل الفحص ولفترة عدة أيام بعد الفحص.
- لا يجوز تناول هذا الدواء إذا كنت في فترة الرضاعة.

تحذيرات خاصة تتعلق بإستعمال الدواء

! يجب إبلاغ الطبيب قبل البدء بالعلاج إذا:
- إذا كنت تعاني من مشكلة في القلب. لقد تطور قصور في القلب لدى أشخاص معينين يعانون من سكري من نوع ٢ على مدى سنين كثيرة ومن أمراض قلبية أو سكتة دماغية والذين تناولوا بيوچليتازون بمشاركة إينسولين. يجب إبلاغ الطبيب بأسرع وقت ممكن إذا كنت تشعر بعلامات قصور قلب كضيق في التنفس غير عادي أو زيادة حادة في وزن الجسم أو وذمة موضعية (إنتفاخ).
- إذا كنت تعاني من إحتباس سوائل أو إذا كنت تعاني من قصور في القلب، خاصة لدى معالجين فوق عمر ٧٥ سنة.

  إذا كنت تتناول أدوية مضادة للإلتهابات التي قد تؤدي أيضاً لإحتباس السوائل ولإنتفاخ، عليك أيضاً إستشارة الطبيب.
- إذا كنت تعاني من مرض عينين يمّيز مرضى السكري، يسمى Macular oedema (إنتفاخ في القسم الخلفي للعين).
- إذا كنت مقدماً على إجراء عملية جراحية بتخدير عام ـ هناك حاجة لإيقاف العلاج بـ كومبيتاكت لفترة عدة أيام قبل العملية وبعدها.
- كنت تعانين من متلازمة المبيض متعدد الكيسات. حيث أن كومبيتاكت قد يسبب الإباضة ويزيد فرص الحمل.

  لتجنب حصول حمل غير مخطط له، ينصح بإستعمال مستحضرات لمنع الحمل.
- إذا كنت تعاني من مشكلة في الكبد. قبل بدء العلاج بـ كومبيتاكت وخلاله يجب القيام بفحوصات دم لفحص أداء الكبد. إذا كنت تشعر بأعراض تدل على مشكلة في الكبد (كالشعور بالمرض دون سبٍب واضح، تقيؤات، ألم في البطن، إرهاق، إنخفاض الشهية للطعام و/أو بول داكن)، يجب مراجعة الطبيب حالاً لتقييم وضعك.
- إذا كنت تتناول أدوية أخرى للسكري، يجب إتخاذ وسائل الحذر لمنع تطور حالة نقص نسب السكر في الدم (hypoglycaemia).
- يجب إجراء فحوص دم بوتيرة تُحدد من قبل الطبيب المعالج بسبب إمكانية إنخفاض في تعداد الدم (فقر دم).
- شوهد عدد مرتفع لكسور في العظام لدى المرضى المعالجين بـ بيوچليتازون، خاصة لدى النساء. يجب إستشارة الطبيب.
- يجري الطبيب المعالج الفحوص لتقييم نجاعة العلاج بـ كومبيتاكت ٣ حتى ٦ أشهر بعد بدء العلاج.

! إذا كنت تتناول أو إذا تناولت مؤخراً أدوية أخرى بما في ذلك أدوية بدون وصفة طبية وإضافات غذائية، إحك للطبيب أو الصيدلي عن ذلك.

يجب إبلاغ الطبيب بالأخص إذا كنت تتناول الأدوية التالية:
- چمفيبروزيل (لخفض الكولسترول)
- ريفامپيسين (لعلاج السل وتلوثات أخرى)
- سيميتيدين (للقرحة)
- چلوكوكورتيكوئيدات (لعلاج الإلتهابات)
- مقلدات بيتا ـ ٢ (لعلاج الربو)
- مدرات بولية (لتخفيض نسب السوائل الزائدة في الجسم)
- مثبطات ACE (لإرتفاع ضغط الدم)

في حال إنك تتناول إحدى هذه الأدوية، يجب فحص مستويات السكر في الدم، لتقييم الجرعة الملائمة من كومبيتاكت.

! إستعمال متزامن مع طعام وشراب

يوصى بتناول الدواء مع الطعام أو بعده حالاً (لتقليل الخطورة لحدوث ألم في البطن).

يجب الإمتناع عن شرب الكحول أو تناول أدوية تحوي كحول، لأن الكحول قد يزيد الخطورة لحدوث حماض لبني ـ lactic acidosis (أنظر فقرة ٤ "أعراض جانبية").

! الحمل والإرضاع

لا يجوز إستعمال هذا الدواء إذا كنت في فترة الحمل أو تخططين للحمل.

لا يجوز إستعمال هذا الدواء إذا كنت في فترة الرضاعة أو تخططين للإرضاع.

! الإستعمال لدى الأطفال

هذا الدواء غير موصى به للإستعمال لدى أطفال دون عمر ١٨ سنة.

! السياقة وإستعمال الماكنات

الدواء لا يمس بقدرة القيادة أو بالقدرة على تشغيل آلات، لكن يجب الحذر إذا كنت تشعر بخلل في الرؤية خلال العلاج.

٣) كيفية إستعمال الدواء؟

يجب إستعمال الدواء حسب تعليمات الطبيب دائماً. عليك الإستيضاح من الطبيب أو الصيدلي إذا لم تكن واثقاً.

الجرعة الدوائية حسب تعليمات الطبيب فقط.

يجب إستعمال هذا الدواء في أوقات محددة حسب ما حُدد من قبل الطبيب المعالج.

الجرعة الدوائية:

الجرعة الدوائية وطريقة العلاج يحددان من قبل الطبيب فقط.

PATIENT PACKAGE INSERT IN ACCORDANCE WITH
THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The dispensing of this medicine is upon doctor's prescription only.

Competact 15 mg/850 mg
Film-coated tablets

Composition of active ingredients
Each tablet contains:
Pioglitazone (as HCl) 15 mg
Metformin HCl 850 mg

For a list of the inactive ingredients in this preparation, see section 6 – "Further information".

Read the package insert carefully and in its entirety before using the medicine. This package insert includes concise information about the medicine. If you have further questions, refer to your doctor or to a pharmacist.

This medicine was prescribed to treat your ailment. Do not pass it on to others. It may harm them, even if their medical state seems similar to yours.

This medicine is not intended for use in children under 18 years of age.

1. WHAT IS THIS MEDICINE INTENDED FOR?
This medicine is intended for the treatment of type 2 diabetes (non-insulin dependent) in adults whose blood sugar levels cannot be controlled by metformin alone.
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.
Competact helps control the level of sugar in your blood by improving the response of the body's cells to insulin that your body produces.

Therapeutic Group
Pioglitazone belongs to the Thiazolidinedione group.
Metformin belongs to the Biguanide group.

2. BEFORE USING THE MEDICINE

☒ Do not use the medicine if:
- Do not use this medicine if you are allergic (hypersensitive) to pioglitazone, metformin or any of the other ingredients of Competact.
- Do not use this medicine if you have heart failure or have had heart failure in the past.
- Do not use this medicine if you recently had a heart attack, have severe circulatory problems, or breathing difficulties.
- Do not use this medicine if you have liver disease.
- Do not use this medicine if you drink alcohol excessively (either every day or only from time to time).
- Do not use this medicine if you have diabetic ketoacidosis (a complication of diabetes with rapid weight loss, nausea or vomiting).
- Do not use this medicine if you have or have ever had bladder cancer.
- Do not use this medicine if you have blood in your urine that your doctor has not diagnosed.
- Do not use this medicine if you have a problem with your kidneys.
- Do not use this medicine if you have a severe infection or are dehydrated.
- Do not use this medicine if you are going to have an X-ray with an injectable dye - in this case you will need to stop taking Competact before the procedure and for a few days after the procedure.
- Do not use this medicine if you are breastfeeding.

Special warnings regarding use of this medicine
❗ Inform the doctor before using this medicine if:
- 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 in patients over 75 years old.
  If you are taking anti-inflammatory medicines that may also cause fluid retention and swelling, you should also consult the doctor.
- If you have a special type of diabetic eye disease called Macular Oedema (swelling of the back of the eye).
- If you are going to have an operation under general anaesthetic - you will need to stop taking Competact for a couple of days before and after the procedure.
- If you have polycystic ovary syndrome. Competact may cause you to ovulate and increase the chance of becoming pregnant. Use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- If you have a problem with your liver. Before you start taking Competact and in the course of treatment you will have a blood sample taken to check your liver function. If you develop symptoms suggesting a problem with your liver (like feeling sick without explanations, vomiting, abdominal pain, tiredness, loss of appetite and/or dark urine), refer to the doctor as soon as possible so as to evaluate your condition.
- If you take Competact with other medicines for diabetes, precautionary measures should be taken in order to prevent low sugar blood level (hypoglycaemia).
- You should undergo blood tests at a frequency to be determined by the doctor as there may be a reduction in blood count (anaemia).
- A higher number of bone fractures were seen in patients treated with pioglitazone, particularly in women. Consult your physician.
- Your doctor will check whether Competact is working 3 to 6 months after you start treatment.

❗ If you are taking or have recently taken other medicines, tell your doctor or pharmacist, including non-prescription medicines or dietary supplements.
Inform your doctor especially if you are taking a medicine from one of the following groups:
- Gemfibrozil (used to lower cholesterol)
- Rifampicin (used to treat tuberculosis and other infections)
- Cimetidine (for ulcer)
- Glucocorticoids (used to treat inflammation)
- Beta-2-agonists (used to treat asthma)
- Diuretics (used to reduce excess water in the body)
- Angiotensin-converting enzyme (ACE) inhibitors (used to treat high blood pressure)

In case you are taking any of these medicines, your blood sugar will be checked, in order to decide the correct dose of Competact.

❗ Taking Competact with food and drink
You may take your tablets with or just after food (to reduce the chance of an upset stomach). Avoid alcohol or medicines containing alcohol while taking Competact since alcohol may increase the risk of lactic acidosis (see section 4 "Side effects").

❗ Pregnancy and Breastfeeding
Do not use this medicine if you are pregnant or are planning to become pregnant.
Do not use Competact if you are breastfeeding or are planning to breastfeed.

❗ Use in children
Use in children under 18 years is not recommended.

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

3. HOW SHOULD YOU USE THIS MEDICINE?
Always follow the doctor's instructions when using this medicine. If you are unsure, refer to your doctor or pharmacist.
Dosage is according to doctor's instructions only.
This medicine is to be taken at specific time intervals as determined by the attending doctor.

Dosage:
Dosage and treatment manner are according to doctor's instructions only.
The usual dosage is as follows:
One tablet of Competact taken twice daily. If necessary your doctor may tell you to take a different dose.
Do not exceed the recommended dosage.
You should swallow the tablets with a glass of water. It is recommended to take your tablets with food.
If you are following a diabetic diet, you should continue with this while you are taking Competact.

Tests and monitoring
- Your weight should be checked at regular intervals. If your weight increases, inform your doctor.
- You should have blood tests periodically during treatment with Competact in order 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 accidentally took an overdose of this medicine or if a child accidentally swallowed this medicine, refer to your doctor or a hospital emergency room immediately and bring the package of the medicine with you.
Effects of overdose:
In such a case, your blood sugar level could fall below the normal level and can be increased by taking sugar. It is recommended that you carry some sugary food (such as sugar lumps, sweets, biscuits or sugary juice).

If you forgot to take the medicine at the required time, take the next dose at its regular time. Do not take two doses together to make up for a forgotten dose.

Be sure to adhere to the treatment as recommended by the doctor, even if your medical state has improved. Do not stop taking this medicine before consulting with your doctor or pharmacist.

4. SIDE EFFECTS
Like all medicines, Competact can cause side effects among some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.
- Very rarely patients taking metformin (one of the active substances of Competact) have experienced a condition called lactic acidosis (excess of lactic acid in your blood), particularly those whose kidneys are not working properly. Symptoms include feeling cold and uncomfortable, severe nausea and vomiting, abdominal pain, unexplained weight loss, or rapid breathing. **If you experience any of these symptoms, stop taking Competact and consult a doctor immediately.**
- Bladder cancer has been experienced uncommonly (1 to 10 users in 1,000) in patients taking Competact. 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.
- Blurred vision due to swelling (or fluid) at the back of the eye has been reported at an unknown frequency. If you experience these symptoms for the first time talk to your doctor as soon as possible. If you already have blurred vision and the symptoms get worse, talk to your doctor as soon as possible.
- Allergic reactions have been reported (frequency not known) in patients taking Competact. 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 as soon as possible.

Additional side effects
Very common side effects (affects more than 1 user in 10):
- abdominal pain
- nausea
- vomiting
- diarrhoea
- loss of appetite

Common side effects (affects 1 to 10 users in 100):
- localised swelling (oedema)
- weight gain
- headache
- respiratory infection
- abnormal vision
- joint pain
- impotence
- blood in urine
- reduction in blood count (anaemia)
- numbness sensation
- taste disturbance
- bone fracture

Uncommon side effects (affects 1 to 10 users in 1,000):
- inflammation of the sinuses (sinusitis)
- gas
- difficulty sleeping (insomnia)

Very rare side effects (affects less than 1 user in 10,000):
- decrease in amount of vitamin B_{12} in the blood
- lactic acidosis (excess of lactic acid in your blood)
- redness of the skin
- itchy skin
- raised, red and itchy rash (hives)

Side effects with unknown frequency (frequency can not be estimated from the available data):
- blurred vision due to swelling (or fluid) in the back of the eye
- inflammation of the liver (hepatitis)
- impaired function of the liver (changes in liver enzymes)
- allergic reactions

Consult with your doctor if any of these side effects worsens, or if you experience a side effect not mentioned in this leaflet.

5. HOW TO STORE THIS MEDICINE?
Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach of children and/or infants in order to avoid poisoning.
Do not induce vomiting unless explicitly instructed to do so by the doctor.
Do not take medicines in the dark! Check the label and the dose each time you take the medicine. Wear glasses if you need them.
Do not take this medicine after the expiration date (Expiry date) indicated on the package. The expiration date refers to the last day of the indicated month.
Store in a dry place, below 25°C.

6. FURTHER INFORMATION
Aside from the active ingredient, this medicine also contains:
Microcrystalline cellulose, Povidone, Croscarmellose sodium, Magnesium stearate, Hypromellose, Macrogol 8000, Talc, Titanium dioxide.
Each tablet contains 3.3-5 mg sodium.

What the medicine looks like and contents of the package
Each package contains 56 tablets.
Tablet shape: the tablets are white oblong, convex, embossed '15 / 850' on one face and '4833M' on the other.

License Holder
Abic Marketing Ltd., P.O. Box 8077, Nathanya 42504.

Name and Address of Manufacturer
Takeda Pharma A/S, Denmark

This leaflet was checked and approved by the Ministry of Health in November 2013.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 150.65.33826.00.

COMP CTAB PL SH 120114

طريقة الإستعمال الإعتيادية عادة هي كما يلي:
يجب تناول قرص واحد من كومبيتاكت مرتين في اليوم. إذا دعت الحاجة يقرر الطبيب بشأن جرعة مختلفة.
لا تتجاوز الجرعة الموصى بها.
يجب بلع الأقراص مع كأس من الماء. يوصى بتناول القرص مع الطعام.
إذا كنت تخضع لحمية خاصة لمرضى السكري، يجب المواظبة عليها طوال فترة تناول كومبيتاكت.

فحوصات ومتابعة
- يجب متابعة وزن جسمك بوتيرة ثابتة. في حال وجود زيادة في وزن الجسم يجب إستشارة الطبيب.
- يجب القيام بفحوصات دم دورية خلال إستعمال كومبيتاكت من أجل مراقبة سلامة وظائف الكبد.
- أثناء فترة العلاج يجب إجراء فحوص وظائف الكلية على الأقل مرة في السنة (إذا كنت مسناً أو تعاني من مشاكل في الكلية يجب إجراء الفحص لفترات أقرب).

إذا تناولت جرعة مفرطة أو إذا بلع طفل بالخطأ من الدواء، يجب التوجه فوراً للطبيب أو لغرفة الطوارىء في المستشفى وإحضار عبوة الدواء معك.

أعراض الجرعة المفرطة:
في هذه الحالة يمكن أن تنخفض مستويات السكر في الدم زيادة عن الحد. يمكن رفع مستوى السكر في الدم من خلال تناول طعام غني بالسكر. يُنصح المعالَج بأن يحمل معه طعام يحوي سكر (مثل: سكاكر، حلويات، كعك أو عصير محلى).

إذا نسيت تناول الدواء في الوقت المطلوب، تناول الجرعة التالية في الوقت المعتاد. لا يجوز تناول جرعتين معاً للتعويض عن الجرعة المنسية.

يجب المواظبة على العلاج حسب ما أوصيت من قبل الطبيب، حتى ولو طرأ تحسن على حالتك الصحية، لا يجوز التوقف عن العلاج بدون إستشارة الطبيب أو الصيدلي.

٤) الأعراض الجانبية
كما بكل دواء، إن إستعمال كومبيتاكت قد يسبب أعراضاً جانبية عند بعض المستعملين. لا تندهش من قائمة الأعراض الجانبية. من الجائز ألا تعاني أياً منها.
- لدى معالَجين يتناولون ميتفورمين (أحد مركبات كومبيتاكت) قد تتطور بصورة نادرة جداً حالة حماض لبني (زيادة حمض اللبن في الدم) خاصةً لدى معالجين مصابين بخلل في وظائف الكلية. الأعراض تشمل شعور بالبرد وقلة الإرتياح، غثيان وتقيؤات شديدة، ألم في البطن، إنخفاض في الوزن غير واضح السبب أو تنفس سريع. **إذا كنت تشعر بإحدى هذه الأعراض، يجب التوقف عن تناول كومبيتاكت ومراجعة الطبيب حالاً.**
- قد يحدث سرطان المثانة بصورة غير شائعة (وتيرة ١ حتى ١٠ من بين ١٠٠٠ معالَج) لدى معالَجين يتناولون كومبيتاكت. علامات وأعراض تشمل دم في البول، ألم عند التبول أو إلحاح فجائي على التبول. في حال أنك تشعر بواحد من هذه الأعراض، يجب إستشارة الطبيب بأسرع وقت ممكن.
- بُلِغ عن رؤية مشوشة في أعقاب إنتفاخ (أو سوائل) في القسم الخلفي من العين شيوعها غير معروف. في حال شعورك بهذه الظاهرة لأول مرة يجب إستشارة الطبيب بأسرع وقت ممكن. في حال أنك تعاني من رؤية مشوشة وطرأ تفاقم في الأعراض يجب التوجه إلى الطبيب بأسرع وقت ممكن.
- لدى معالَجين تناولوا كومبيتاكت، بلغ عن حالات (وتيرة غير معروفة) لردود فعل آليرجية. في حال أنك تشعر برد فعل آليرجي خطير، يشمل شرى (حكة) وإنتفاخ في الوجه، في الشفتين، في اللسان أو في الحنجرة ممّا قد يسبب صعوبات في التنفس أو البلع، عليك التوقف عن الدواء وإستشارة الطبيب بأسرع وقت ممكن.

أعراض جانبية إضافية
أعراض جانبية شائعة جداً (تؤثر على أكثر من ١ حتى ١٠ معالَجين):
- ألم في البطن
- غثيان
- تقيؤات
- إسهال
- إنخفاض الشهية للطعام

أعراض جانبية شائعة (تؤثر على ١ حتى ١٠ من بين ١٠٠ معالَج):
- إنتفاخ موضعي (وذمة)
- زيادة في الوزن
- صداع
- إلتهابات في جهاز التنفس
- خلل في الرؤية
- ألم في المفاصل
- عجز جنسي (impotence)
- دم في البول
- إنخفاض بتعداد خلايا الدم (فقر دم)
- إنعدام الحس (شعور بالتنميل)
- إضطرابات في حاسة المذاق
- كسور في العظام

أعراض جانبية غير شائعة (تؤثر على ١ حتى ١٠ من بين ١٠٠٠ معالَج):
- إلتهاب في الجيوب الأنفية (sinusitis)
- نفخة (غازات)
- أرق

أعراض جانبية نادرة جداً (تؤثر على أقل من ١ من بين ١٠٠٠٠ معالَج):
- إنخفاض نسبة ڤيتامين B_{12} في الدم
- حماض لبني (زيادة حمض اللبن في الدم)
- إحمرار الجلد
- حكة في الجلد
- طفح يشمل آفات حمراء، بارزة وحاكة (شرى)

أعراض جانبية ذات شيوع غير معروف (لا يمكن تحديد الوتيرة حسب المعطيات الموجودة):
- رؤية مشوشة نتيجة إنتفاخ (أو سوائل) في القسم الخلفي للعين
- إلتهاب في الكبد (hepatitis)
- خلل في وظائف الكبد (تغيرات في نسب خمائر الكبد)
- ردود فعل آليرجية

إذا تفاقمت إحدى الأعراض الجانبية، أو عندما تعاني من عرض جانبي لم يذكر في هذه النشرة، عليك إستشارة الطبيب.

٥) كيفية تخزين الدواء؟
تجنب التسمم! يجب حفظ هذا الدواء وكل دواء في مكان مغلق بعيداً عن متناول أيدي الأطفال و/أو الرضع، وذلك لتفادي إصابتهم بالتسمم. لا تسبب التقيؤ بدون تعليمات صريحة من الطبيب.
لا تتناول أدوية في العتمة! يجب تشخيص طابع الدواء والتأكد من المقادير الدوائية في كل مرة تتناول فيها دواء.
ضع النظارات الطبية إذا لزم الأمر ذلك.
لا يجوز إستعمال الدواء بعد إنقضاء تاريخ الصلاحية (Expiry date) الذي يظهر على ظهر العلبة. يشير تاريخ الصلاحية الى اليوم الأخير من نفس الشهر.
يجب التخزين في مكان جاف، دون ٢٥ درجة مئوية.

٦) معلومات إضافية
يحتوي الدواء بالإضافة للمادة الفعالة أيضاً:
Microcrystalline cellulose, Povidone, Croscarmellose sodium, Magnesium stearate, Hypromellose, Macrogol 8000, Talc, Titanium dioxide.

كل قرص كومبيتاكت يحتوي: ٣,٣–٥ ملغ صوديوم.

كيف يبدو الدواء وما هو محتوى العلبة
تحتوي العلبة على ٥٦ قرصاً.
شكل القرص: قرص محدب مطاول بلون أبيض، يظهر بأحد جانبيه العدد "15/850" وفي الجانب الثاني يظهر "4833M".

صاحب الإمتياز: أبيك للتسويق م.ض.، ص.ب ٨٠٧٧، نتانيا ٤٢٥٠٤

اسم المنتج وعنوانه Takeda Pharma A/S, Denmark.

أقرت وزارة الصحة صيغة هذه النشرة ومحتواها فُحص ورُخص في تاريخ: تشرين الثاني ٢٠١٣

رقم سجل الدواء في سجل الأدوية الحكومي في وزارة الصحة: ١٥٠ ٦٥ ٣٣٨٢٦ ٠٠

من أجل سهولة وتهوين القراءة، تمت صياغة هذه النشرة بصيغة المذكر. على الرغم من ذلك، فإن الدواء مخصص لكلا الجنسين.