SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bezafibrate Medomie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400mg of bezafibrate

Excipients with known effect
Each 400mg tablet contains 46.4 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sustained-release tablet for oral use.
White to off-white coloured, round, biconvex, coated tablets, debossed "J9" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Bezafibrate Medomie is indicated as an adjunct to diet and other non- pharmacological treatment (e.g. exercise, weight reduction) for the following:
- Treatment of severe hypertriglyceridaemia

4.2 Posology and method of administration

Adults

The recommended dosage for Bezafibrate Medomie is one tablet, equivalent to 400mg bezafibrate and should be swallowed whole with sufficient fluid after a meal either in the morning or at night.

Elderly

In elderly patients there is a physiological reduction of the renal function with age. Bezafibrate Medomie should not be prescribed/administered to older people whose creatinine clearance is below 60ml/min (see Renal impairment below).

Paediatric population

At present there is inadequate information regarding an appropriate dose recommendation in children.

Renal impairment

Bezafibrate Medomie is contraindicated in dialysis patients. Bezafibrate should not be given to patients with renal impairment with serum creatinine > 135 micromol/l or creatinine clearance < 60 ml/min. Such patients may be treated with conventional tablets (200mg Bezafibrate) using an appropriately reduced daily dosage.
For patients with a history of gastric sensitivity, the dosage may be gradually increased over 5-7 days to the maintenance level.
The response to therapy is normally rapid, although a progressive improvement may occur over a number of weeks. Treatment should be withdrawn if an adequate response has not been achieved within 3 to 4 months.

4.3 Contraindications

- Hypersensitivity to the active substance, other fibrates, or to any of the excipients listed in section 6.1.
- Significant hepatic disease (other than fatty infiltration of the liver associated with raised

triglyceride values).
- Gall-bladder diseases with or without cholelithiasis.
- Patients with nephrotic syndrome and severe renal failure (serum creatinine > 135µmol/l; creatinine clearance <60ml/min) and patients undergoing dialysis (see section 4.2).
- Combination therapy (concomitant use) of bezafibrate with HMG CoA reductase inhibitors (statins) in patients with predisposing factors for myopathy (see sections 4.4. and 4.5)
- Known photoallergic or phototoxic reactions to fibrates.

4.4 Special warnings and precautions for use

- Bezafibrate should be used as an adjunct to diet and measures such as physical activity, weight loss and adequate treatment of other metabolic disorders (e.g. diabetes, gout).
- Secondary causes of dyslipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism should be adequately treated before Bezafibrate therapy is initiated.
- Bezafibrate and other fibrates may cause myopathy, manifested as muscle weakness or pain, often accompanied by a considerable increase in creatine kinase (CPK). In isolated cases severe muscle damage (rhabdomyolysis) has been observed. The risk of rhabdomyolysis may be increased when higher than recommended doses of bezafibrate are used, most frequently in the presence of impaired renal function and in patients with predisposing factors for myopathy, (including renal impairment, elderly (aged >65 years), personal of familial history of hereditary muscular disorders and previous history of muscular toxicity with a fibrate or other lipid lowering drugs, hypothyroidism, severe infection, trauma, surgery, disturbances of hormone or electrolyte imbalance and a high alcohol intake).
- Bezafibrate should be used with caution in combination with HMG CoA reductase inhibitors as the combination of HMG CoA inhibitors and fibrates has been shown to increase the incidence and severity of myopathy. Patients should be informed of symptoms and monitored for signs of myopathy and increased CPK activity and combination therapy discontinued if signs of myopathy develop. Combination therapy should not be used in patients with predisposing factors for myopathy (see section 4.3 and 4.5).
- Bezafibrate alters the composition of bile. There have been isolated reports of the development of gallstones.
- As bezafibrate could cause cholelithiasis appropriate diagnostic procedures should be performed if cholelithic symptoms and signs occur (see section *4.8 Undesirable effects).*
- Since oestrogens may lead to a rise in lipid levels, the prescribing of bezafibrate in patients taking oestrogens or oestrogen-containing contraceptives must be critically considered on an individual basis.
- When bezafibrate is given in combination with anion-exchange resins (e.g. colestyramine), the two drugs should be taken at least 2 hours apart.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions:

Care is required in administering Bezafibrate Medomie to patients taking coumarin-type anticoagulants, the action of which may be potentiated. The dosage of anticoagulant should be reduced by up to 50% and readjusted by monitoring blood coagulation.

As bezafibrate improves glucose utilisation the action of antidiabetic medication, including insulin, may be potentiated. Hypoglycaemia has not been observed although increased monitoring of the glycaemic status may be warranted for a brief period after introduction of Bezafibrate Medomie .

Should combined therapy with an ion-exchange resin be considered necessary, there should be an interval of 2 hours between the intake of the resin and Bezafibrate Medomie as the absorption of bezafibrate otherwise may be impaired.

In isolated cases, a pronounced though reversible impairment of renal function (accompanied by a corresponding increase in serum creatinine level) has been reported in organ transplant patients receiving immuno-suppressant therapy and concomitant bezafibrate. Accordingly,

renal function should be closely monitored in these patients and, in the event of relevant significant changes in laboratory parameters, bezafibrate should if necessary, be discontinued. MAO-inhibitors (with hepatotoxic potential) should not be administered together with bezafibrate.
Interaction between HMG CoA reductase inhibitors and fibrates may vary in nature and intensity depending on the combination of the administered drugs. A pharmacodynamic interaction between these two classes of drugs may, in some cases, also contribute to an increase in the risk of myopathy (see section 4.3 and 4.4) for specific dose recommendations of statins refer also to the SPC of the relevant product.

4.6 Fertility, pregnancy and lactation

Fertility
There is insufficient information available on the effects of Bezafibrate tablets on human fertility. Animal fertility studies with bezafibrate have shown no indication of reduced fertility.

Pregnancy
There are limited data from the use of bezafibrate in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Bezafibrate Medomie is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation
There is insufficient information on the excretion of bezafibrate or its metabolites in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bezafibrate Medomie therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machine:

Bezafibrate Medomie have been shown to cause dizziness and can have a minor to moderate effect on the ability to drive or use machines. Patients should not drive or use machines if they are affected.

4.8 Undesirable effects

The overall safety profile of bezafibrate is based on a combination of clinical study data and post-marketing experience.

The frequency of adverse drug reactions (ADRs) according to MedDRA System Organ Class is displayed in the table below. Frequency of reporting: Very common (≥1/10), Common (≥ 1/100 to <1/10), Uncommon (≥ 1/1,000 to <1/100), Rare (≥ 1/10,000 to <1/1000), Very rare (<1/10,000).

Blood and lymphatic system disorders:
Very rare: Pancytopenia, thrombocytopenic purpura.

Immune system disorders:
Uncommon: Hypersensitivity reactions including anaphylactic reactions.

Metabolism and nutrition disorders:
Common: Decreased appetite.

Nervous system disorders:
Uncommon: Dizziness, headache.
Rare: Peripheral neuropathy, paraesthesia.

Psychiatric disorders:
Rare: Depression, insomnia.

Gastrointestinal disorders:
Common: Gastrointestinal disorders.
Uncommon: Abdominal pain, constipation, dyspepsia, abdominal distension, diarrhoea, nausea.
Rare: Pancreatitis

Hepatobiliary disorders:
Uncommon: Cholestasis.
Very rare: Cholelithiasis.

Skin and subcutaneous tissue disorders:
Uncommon: Pruritus, urticaria, photosensitivity reaction, alopecia, rash.
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders:
Uncommon: Muscular weakness, myalgia, muscle cramp. Very rare: Rhabdomyolysis.

Renal and urinary disorders:
Uncommon: Acute renal failure.

Reproductive system and breast disorders:
Uncommon: Erectile dysfunction NOS.

Respiratory, thoracic and mediastinal disorders:
Very rare: Interstitial lung disease.

Investigations:
Uncommon: Increased blood creatinine phosphokinase, blood creatinine increased, decreased gamma-glutamyl transferase and in parallel alkaline phosphatase
Very rare: Haemoglobin decreased, platelet increased, white blood cell count decreased, gamma-glutamyl transferase increased, transaminase increased.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose
No specific effects of acute overdose are known apart from rhabdomyolysis. There is no specific antidote. Thus, appropriate symptomatic therapy is recommended in cases of overdose. In cases of rhabdomyolysis, bezafibrate must be stopped immediately and renal function carefully monitored.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC Code: C10AB02

Mechanism of Action:
Bezafibrate lowers elevated blood lipids (triglycerides and cholesterol). Elevated VLDL and LDL are reduced by treatment with bezafibrate, whilst HDL-levels are increased. The activity of triglyceride lipases (lipoprotein lipase and hepatic lipoprotein lipase) involved in the catabolism of triglyceride-rich lipoproteins is increased by bezafibrate. In the course of the intensified degradation of triglyceride-rich lipoproteins (chylomicrons, VLDL), precursors for the formation of HDL are formed which explains an increase in HDL. Furthermore, cholesterol biosynthesis is reduced by bezafibrate, which is accompanied by a stimulation of the

LDL-receptor mediated lipoprotein catabolism.
Studies have shown bezafibrate to be effective in treating hyperlipidaemia in patients with diabetes mellitus. Some cases showed a beneficial reduction in fasting blood glucose.
Significant reductions in serum fibrinogen levels have been observed in hyperfibrinogenaemic patients treated with bezafibrate.
There is evidence that treatment with fibrates may reduce coronary heart disease events, but they have not been shown to decrease all-cause mortality in the primary or secondary prevention of cardiovascular disease.

Efficacy / Clinical Studies:
No data available.

5.2 Pharmacokinetic properties:

Absorption:
Bezafibrate is rapidly and almost completely absorbed from the standard tablet formulation. A peak plasma concentration of about 14mg/L is reached after 2 hours following ingestion of 2 x 200 mg standard tablets given as a single dose in healthy volunteers. With Bezafibrate Medomie, a peak concentration of about 8 mg is reached after about 4 hours. The relative bioavailability of bezafibrate retard compared to the standard form is about 70%.

Distribution
The protein-binding of bezafibrate in serum is approximately 95% and the apparent volume of distribution is 17 litres.

Biotransformation:
50% of the administered bezafibrate dose is recovered in the urine as unchanged drug and 20% in the form of glucuronides.

Elimination:
Elimination is rapid, with excretion almost exclusively renal. Ninety-five percent of the activity of the 14C-labelled drug is recovered in the urine and 3% in the faeces within 48 hours. 50% of the applied dose is recovered in the urine as unchanged drug and 20% in form of glucuronides. The rate of renal clearance ranges from 3.4 to 6.0L/h. The apparent elimination half-life of bezafibrate prolonged-release tablets are about 2-4 hours.

Pharmacokinetics in Special Populations:
Pharmacokinetic investigations in the elderly suggest that elimination may be delayed in cases of impaired liver function. Liver disease (except fatty liver) is a contraindication for the use of bezafibrate (see 4.3 Contraindications).
In elderly patients, there is a physiological reduction of the renal function with age.
Bezafibrate dosage should be adjusted based on the serum creatinine and creatinine clearance values as indicated in the above table. (see section 4.2).
The elimination of bezafibrate is reduced in patients with impaired renal function and dosage adjustments are necessary to prevent drug accumulation and toxic effects. (see section 4.2) Not surprisingly there is a correlation between creatinine clearance and the elimination half-life of bezafibrate; with decreasing creatinine clearance the elimination half-life is increasing. Because of its high protein binding, bezafibrate cannot be dialysed (cuprophane filter). The use of bezafibrate is contraindicated in dialysis patients.

5.3 Preclinical safety data

The chronic administration of a high dose of bezafibrate to rats was associated with hepatic tumour formation. This dosage was in the order of 30 to 40 times the human dosage. No such effect was apparent at reduced intake levels approximating more closely to the lipid-lowering dosage in humans. There was, however, no indication of reduced fertility in the rat at human equivalent doses that are 5 to 11-fold higher than the proposed clinical dose of 600 mg per day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hypromellose (HMPC K100 LV)
Lactose monohydrate
Povidone (K-30)
Magnesium stearate
Colloidal anhydrous silica
Sodium lauryl sulphate

C*oating:*
Purified talc
Lactose monohydrate
Titanium dioxide
Hypromellose (HPMC E-5)
Macrogol (PEG 8000)
Polysorbate 80
Sodium citrate
Eudragit NE 30 D

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C. Protect from moisture.

6.5 Nature and contents of container

Pack of 30 tablets
PVC-Alu blister strips

6.6 Special precautions for disposal

No special requirements for disposal.

7. MANUFACTURER

Medreich Limited (Unit 3)
survey No 4/3, Avalahalli, Anjanapura, Bangalore, Karnataka, India, 560062

8. LICENSE HOLDER

Medomie Pharma Ltd., POB 742, Givatayim, 5310602, Israel

9. REGISTRATION NUMBER

176-67-37746-99

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