SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acrose 50
Acrose 100

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Acrose 50
Each **Acrose 50** tablet contains 50mg Acarbose.
Acrose 100
Each **Acrose 100** tablet contains 100mg Acarbose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Acrose 50 are round, biconvex, white to yellowish tablets.
Acrose 100 are round, biconvex, white to yellowish tablets, with one central score line on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of non-insulin dependent (NIDDM) diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

4.2 Posology and method of administration

Dosage

Adults

The recommended initial dose is 50mg three times a day. However, some patients may benefit from more gradual initial dose titration to minimise gastrointestinal side effects. This may be achieved by initiating treatment at 50mg once or twice a day, with subsequent titration to a three times a day regimen.

If after six to eight weeks' treatment patients show an inadequate clinical response, the dosage may be increased to 100mg three times a day. A further increase in dosage to a maximum of 200mg three times a day may occasionally be necessary.
Acrose tablets are intended for continuous long-term treatment.

If adverse events occur in spite of strict adherence to the diabetic diet, the dose should not be increased and if necessary should be reduced (see section 4.8).

Elderly patients

No modification of the normal adult dosage regimen is necessary.

Children and adolescents under 18 years

The efficacy and safety of **Acrose** in children and adolescents have not been established. **Acrose** is not intended for use in patients under the age of 18 years.

Renal or hepatic impairment

See section 4.3.

Method of administration

Acrose tablets are taken orally and should be chewed with the first mouthful of food, or swallowed whole with a little liquid directly before the meal. Owing to the great individual variation of glucosidase activity in the intestinal mucosa, there is no fixed dosage regimen, and patients should be treated according to clinical response and tolerance of intestinal side effects.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Acrose tablets are also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, **Acrose** tablets should not be used in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who suffer from states which may deteriorate as a result of increased gas formation in the intestine, e.g. larger hernias, Roemheld's symptom complex, strictures and ulcers of intestine.

Acrose tablets are contraindicated in patients with severe liver dysfunction (e.g. liver cirrhosis).

As **Acrose** tablets have not been studied in patients with severe renal impairment, it should not be used in patients with a creatinine clearance < 25 ml/min/1.73m².

Acrose tablets are contraindicated during pregnancy and in nursing mothers.

4.4 Special warnings and precautions for use

Hypoglycaemia: When administered alone, **Acrose** does not cause hypoglycaemia. It may, however, act to potentiate the hypoglycaemic effects of insulin and sulphonylurea drugs, and the dosages of these agents may need to be modified accordingly. In individual cases hypoglycaemic shock may occur (i.e. clinical sequelae of glucose levels < 1 mmol/L such as altered conscious levels, confusion or convulsions).

Episodes of hypoglycaemia occurring during therapy must, where appropriate, be treated by the administration of glucose, not sucrose. This is because acarbose will delay the digestion and absorption of disaccharides, but not monosaccharides.

Transaminases: Patients treated with acarbose may, on rare occasions, experience an idiosyncratic response with either symptomatic or asymptomatic hepatic dysfunction. In the majority of cases this dysfunction is reversible on discontinuation of acarbose therapy. It is recommended that liver enzyme monitoring is considered during the first six to twelve months of treatment. If elevated transaminases are observed, withdrawal of therapy may be warranted, particularly if the elevations persist. In such circumstances, patients should be monitored at weekly intervals until normal values are established.

The administration of antacid preparations containing magnesium and aluminium salts, e.g. hydrotalcite, has been

shown not to ameliorate the acute gastrointestinal symptoms of **Acrose** in higher dosage and should, therefore, not be recommended to patients for this purpose.

If ileus or sub-ileus is suspected, treatment must be stopped immediately (see section 4.8).

It is essential to adhere to a strict diabetic diet when taking **Acrose**.

Regular use of **Acrose** should not be interrupted without medical advice as this may lead to a rise in blood glucose.

Since the information available on its effects and tolerability in children and adolescents is still insufficient, **Acrose** should not be used in patients under 18 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

Sucrose (cane sugar) and foods containing sucrose often cause abdominal discomfort or even diarrhoea during treatment with **Acrose** as a result of increased carbohydrate fermentation in the colon.

Intestinal adsorbents (e.g. charcoal) and digestive enzyme preparations containing carbohydrate splitting enzymes (e.g. amylase, pancreatin) may reduce the effect of **Acrose** and should not therefore be taken concomitantly.

The concomitant administration of neomycin may lead to enhanced reductions of postprandial blood glucose and to an increase in the frequency and severity of gastro- intestinal side effects. If the symptoms are severe, a temporary dose reduction of **Acrose** may be warranted.

The concomitant administration of colestyramine may enhance the effects of **Acrose**, particularly with respect to reducing postprandial insulin levels.
Simultaneous administration of **Acrose** and colestyramine should, therefore, be avoided. In the rare circumstance that both **Acrose** and colestyramine therapy are withdrawn simultaneously, care is needed as a rebound phenomenon has been observed with respect to insulin levels in non-diabetic subjects.

In individual cases **Acrose** may affect digoxin bioavailability, which may require dose adjustment of digoxin. Monitoring of serum digoxin levels should be considered.

In a pilot study to investigate a possible interaction between **Acrose** and nifedipine, no significant or reproducible changes were observed in the plasma nifedipine profiles.

Several therapeutic agents including thiazide and other diuretics, corticosteroids, phenothiazines, thyroid hormones, oestrogens and oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers and isoniazid can cause hyperglycaemia, which may attenuate the pharmacodynamic effects of **Acrose**.
Blood glucose levels should be closely monitored if any of these agents are used by patients receiving **Acrose**, or if treatment with **Acrose** is contemplated in patients already receiving any of these agents.

If **Acrose** is prescribed in addition to other oral hypoglycaemic agents (*e.g.* a sulphonylurea or metformin), a fall of the blood glucose into the hypoglycaemic range may necessitate a decrease in the dose of the concomitant medication.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal product for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or fetus, the course of gestation, and peri- and postnatal development.

Acrose should not be used during pregnancy.

When the patient plans to become pregnant and during pregnancy, diabetes should be treated with insulin to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations

associated with abnormal blood glucose levels.

Lactation
It is unknown whether acarbose is excreted in human breast milk. Animal studies have shown excretion of acarbose in breast milk. **Acrose** should not be used during breast-feeding.

Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). No impairment of fertility was observed in animals.

4.7 Effects on ability to drive and use machines

Acrose monotherapy does not cause hypoglycaemia and is therefore unlikely to have effects on the ability to drive or to use machines. However, patients should be informed of the risk of hypoglycaemia when **Acrose** is used in combination with metformin, sulphonylurea or insulin.

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with acarbose sorted by CIOMS III categories of frequency (placebo-controlled studies in clinical trial database: acarbose N = 8,595; placebo N = 7,228; status: 10 Feb 2006) are listed below.

Frequencies are defined as very common (≥1/10); common (>1/100 to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10 000 to <1/1000); very rare (<1/10 000); Not Known.

Blood and the lymphatic system disorders:
Not known (cannot be estimated from the available data): Thrombo-cytopenia*

Immune System Disorders:
Not known (cannot be estimated from the available data): Hypersensitivity/ Allergic reaction (rash, erythema, exanthema, urticaria)*

Vascular Disorders:
Rare: Oedema

Gastrointestinal Disorders:
Very common: Flatulence
Common: Diarrhoea, Gastrointestinal and abdominal pains
Uncommon: Nausea, Vomiting, Dyspepsia
Not known (cannot be estimated from the available data): Subileus/ileus, Pneumatosis cystoidis intestinalis*

Hepatobiliary Disorders:
Uncommon: Transient increase in liver enzymes
Rare: Jaundice
Not known (cannot be estimated from the available data): Hepatitis*

Skin and subcutaneous tissue disorders:
Not known: Acute generalised exanthematous pustulosis

*ADRs derived from post marketing reports (status: 31 Dec 2005).

If ileus or subileus is suspected, treatment must be stopped immediately.

Liver disease, abnormal liver function and liver injury have been reported during post-marketing experience. Individual cases of fulminant hepatitis with fatal outcome have been reported in Japan. The relationship to **Acrose** is unclear.

If the prescribed diabetic diet is not observed the intestinal side effects may be intensified.

If strongly distressing symptoms develop in spite of adherence to the diabetic diet prescribed, the doctor must be consulted and the dose temporarily or permanently reduced.

The gastrointestinal symptoms may be severe and pronounced. In these cases, a decision must be made as to whether to continue treatment with acarbose.

In patients receiving the recommended daily dose of 150 to 300 mg **Acrose**, clinically relevant abnormal liver function tests (three times above upper limit of normal range) were rarely observed. Abnormal values may be transient under ongoing **Acrose** therapy. *(See Section 4.4).*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
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

When **Acrose** tablets are taken with carbohydrate-containing (poly-, oligo-, disaccharides) drinks and/or meals overdose may lead to meteorism, flatulence and diarrhoea. If **Acrose** tablets are taken independently of food, excessive intestinal symptoms need not be anticipated.

No specific antidotes to **Acrose** tablets are known.
Intake of carbohydrate-containing meals or beverages should be avoided for 4-6 hours. Diarrhoea should be treated by standard conservative measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral antidiabetic agent from the class of Alpha- glucosidase inhibitors.
ATC code: A10BF01.

In all species tested, acarbose exerts its activity in the intestinal tract. The action of acarbose is based on the competitive inhibition of intestinal enzymes (α-glucosidases) involved in the degradation of disaccharides, oligosaccharides, and polysaccharides.
This leads to a dose-dependent delay in the digestion of these carbohydrates. Glucose derived from these carbohydrates is released and taken up into the blood more slowly. In this way, acarbose reduces the postprandial rise in blood glucose, thus reducing blood glucose fluctuations. This relieves the beta cells and compensatory postprandial hyperinsulinemia is avoided.

The time of intake of acarbose determines the extent of its effectiveness: the maximum effect is achieved when taken with the first bite of the main meal; intake approx. 30 minutes before the start of the meal, the effect of acarbose is already significantly reduced. However, taking it 15 minutes after the start of a meal hardly affects the effect of acarbose.

In contrast to sulphonylureas, acarbose has no stimulatory action on the pancreas. Even with long-term use, the effect of acarbose does not diminish: the enzymes in the small intestine do not lose activity, and the inhibition by acarbose remains.

Acarbose treatment does not lead to an increase in body weight. Improved insulin sensitivity has been observed in patients with manifest diabetes.
Treatment with acarbose also results in a reduction of fasting blood glucose and to modest changes in levels of glycated

haemoglobin (HbA_1, HbA_{1c}). The changes may be a reduction or reduced deterioration in HbA_1 or HbA_{1c} levels, depending upon the patient's clinical status and disease progression. These parameters are affected in a dose-dependent manner by acarbose.

In a meta-analysis of 7 double-blind placebo-controlled studies with 2,180 type 2 diabetics and a study duration of at least 52 weeks, the risk of cardiovascular events, especially myocardial infarction, decreased significantly with acarbose.

5.2 Pharmacokinetic properties

Following oral administration, only 1-2% of the active inhibitor is absorbed.

The pharmacokinetics of acarbose were investigated after oral administration of the ^{14}C-labelled substance (200mg) to healthy volunteers. On average, 35% of the total radioactivity (sum of the inhibitory substance and any degradation products) was excreted by the kidneys within 96 h. The proportion of inhibitory substance excreted in the urine was 1.7% of the administered dose. 51% of the activity was eliminated within 96 hours in the faeces. The course of the total radioactivity concentration in plasma was comprised of two peaks. The first peak, with an average acarbose- equivalent concentration of 52.2 ± 15.7μg/l after 1.1 ± 0.3 h, is in agreement with corresponding data for the concentration course of the inhibitor substance (49.5 ± 26.9μg/l after 2.1 ± 1.6 h). The second peak is on average 586.3 ± 282.7μg/l and is reached after 20.7 ± 5.2 h. The second, higher peak is due to the absorption of bacterial degradation products from distal parts of the intestine. In contrast to the total radioactivity, the maximum plasma concentrations of the inhibitory substance are lower by a factor of 10-20. The plasma elimination half-lives of the inhibitory substance are 3.7 ± 2.7 h for the distribution phase and 9.6 ± 4.4 h for the elimination phase.

A relative volume of distribution of 0.32 l/kg body-weight has been calculated in healthy volunteers from the concentration course in the plasma. (Intravenous administration, 0.4mg/kg body weight).

5.3 Preclinical safety data

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

A markedly reduced body weight gain in rats and dogs after repeated administration of acarbose was considered as pharmacodynamic effect (loss of carbohydrates) and could be counteracted by increase of food or glucose supplementation.

Carcinogenicity was studied in Sprague-Dawley rats, Wistar rats and hamsters. An increased tumour incidence in certain tissues (kidney, testis) was observed if malnutrition due to acarbose was not corrected. No increase in tumour rate was observed if the body weight gain was kept normal by food or glucose supplementation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, microcrystalline cellulose, magnesium stearate, silica colloidal anhydrous.

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 25 °C.

6.5 Nature and contents of container

30 tablets in transparent PVC/PE/PVDC aluminium blisters.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MANUFACTURER

Bluepharma Industria Farmaceutica S.A., Sao Martino Do Bispo, 3045-016 Coimbra, Portugal.

8 REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O. Box 405, Jerusalem 9100301, Israel.

9 REGISTRATION NUMBER(S)

Acrose 50:142 78 31978 00
Acrose 100:142 79 31979 00

Revised in January 2025.