AUSTRALIAN PRODUCT INFORMATION
ACARBOSE VIATRIS (ACARBOSE) TABLETS

1 NAME OF THE MEDICINE

Acarbose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg or 100mg acarbose.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ACARBOSE VIATRIS 50 mg are round, biconvex, white to off-white tablets, marked with “ACA 50” on one side.

ACARBOSE VIATRIS 100 mg are round, biconvex, white to off-white tablets, marked with a score on one side, and “ACA 100” on the reverse side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

As an adjunct to prescribed diet and exercise for the management of blood glucose concentrations in non-insulin dependent diabetic patients who are inadequately controlled by diet alone or by diet and oral hypoglycaemic agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Since the activity and the tolerability of acarbose varies from individual to individual, the optimal dosage must be individualised.

ACARBOSE VIATRIS should be swallowed whole with a little liquid directly before a meal or chewed with the first few mouthfuls of the meal.

In adults, ACARBOSE VIATRIS should be started at a low initial dose and be increased slowly to minimise the gastrointestinal side effects. Treatment is usually commenced at 50 mg once daily for the first week, 50 mg twice daily for the second week and 50 mg three times a day for the third week. A further increase of the dose may be necessary after 4 - 8 weeks on the basis of the blood glucose level. The average adult dose is 100 mg ACARBOSE VIATRIS three times daily. A further increase to 200 mg ACARBOSE VIATRIS three times daily may occasionally be necessary (see section 4.4 Special warnings and precautions for use).

If gastrointestinal symptoms are not tolerated despite close adherence to the prescribed diet, a reduction in the dose should be considered.

No modification of the adult dosage regimen is necessary in the elderly.

4.3 CONTRAINDICATIONS

Hypersensitivity to acarbose and/or any of the inactive tablet constituents, pregnancy and lactation.

Acarbose should not be used in patients under 18 years of age.

Acarbose is contraindicated in patients with severe renal impairment (creatinine clearance <25 mL/min).

Acarbose is contraindicated in patients with severe hepatic impairment.

Acarbose should not be used in patients with gastrointestinal disorders associated with malabsorption. It should not be used in patients with inflammatory bowel disease (such as ulcerative colitis and Crohn's disease), colonic ulceration, partial intestinal obstruction, or in patients predisposed to intestinal obstruction or ileus.

Acarbose 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. Roemhelds syndrome, major hernias, intestinal obstruction and intestinal ulcers).

Acarbose is contraindicated in patients with diabetic ketoacidosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General
The administration of antacid preparations containing magnesium and aluminium salts has been shown not to ameliorate the acute gastrointestinal symptoms of acarbose in higher dosage and should, therefore, not be recommended to patients for this purpose.

Ingestion of sucrose and food that contains sucrose can easily lead to considerable intestinal symptoms (e.g. flatulence and bloating), or even diarrhoea during treatment with acarbose, as a result of increased carbohydrate fermentation in the colon (see section 4.8 Adverse effects (Undesirable effects)).

Hypoglycaemia: Acarbose has an antihyperglycaemic effect, but does not itself induce hypoglycaemia. If acarbose is prescribed in addition to drugs containing sulfonylureas or metformin or in addition to insulin, a fall of blood glucose levels into the hypoglycaemic range may necessitate a suitable decrease in the sulfonylurea, metformin or insulin dose. In individual cases hypoglycaemic shock may occur. In the event of acute hypoglycaemia, it should be borne in mind that cane sugar (sucrose) is broken down into fructose and glucose more slowly during acarbose treatment and is therefore unsuitable for a rapid elimination of hypoglycaemic phenomena. Glucose (i.e. dextrose) should be used in place of cane sugar (sucrose).

Elevated Serum Transaminase Levels: In clinical trials at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with acarbose was the same as placebo. In long-term studies (up to 12 months, and including acarbose doses up to 300 mg t.i.d.) conducted in the U.S., treatment-emergent elevations of serum transaminases (ALT and/or AST) occurred in 15% of acarbose-treated patients as compared to 7% of placebo-treated patients. The elevations were asymptomatic, reversible, more common in females and in general, were not associated with other evidence of liver dysfunction.

Cases of fulminant hepatitis have been reported during acarbose therapy (see Section 4.8 Adverse effects (undesirable effects). The mechanism is unknown, but acarbose may contribute to a multifactorial pathophysiology of liver injury.

Patients' liver enzyme values should be monitored regularly, preferably at monthly intervals for the first 6 to 12 months after initiation of acarbose therapy. If elevated transaminases are observed, a reduction in dosage or 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.

Use in hepatic impairment
In patients with a known history of liver impairment or liver disease, liver enzymes should be measured prior to the start of acarbose therapy and monitored on a regular basis during the first year. If a clinical deterioration or increases in levels of hepatic enzymes are detected, discontinuation of treatment with acarbose should be considered.

Acarbose is contraindicated in patients with severe hepatic impairment (see Section 4.3 Contraindications).

Use in renal impairment
Plasma concentrations of acarbose in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Treatment of patients with severe renal dysfunction (creatinine clearance <25 mL/min) with acarbose is contraindicated.

Use in the elderly
See section 4.2 Dose and method of administration.

Paediatric use
Since there is insufficient data on the safety and efficacy of acarbose in children, acarbose should not be used in patients under 18 years of age.

Effects on laboratory tests
Small reductions in haematocrit occurred more often in acarbose-treated patients than in placebo-treated patients but were not associated with reductions in haemoglobin. Low serum calcium and low plasma vitamin B6 levels were associated with acarbose therapy but were thought to be either spurious or of no clinical significance.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

General: Certain drugs tend to produce hyperglycaemia and may lead to loss of blood glucose control. These drugs include diuretics (thiazides, furosemide), corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics and isoniazid. When such drugs are administered to a patient receiving acarbose, the patient should be closely monitored for loss of blood glucose control.

Oral antidiabetic agents: When acarbose is prescribed in addition to existing treatment with sulfonylureas, or metformin, the dosage of the sulfonylurea or metformin must be appropriately reduced, should the blood glucose levels fall in the hypoglycaemic range. In individual cases hypoglycaemia-related impairment of consciousness may occur.

Neomycin: Due to neomycin-induced malabsorption of carbohydrate, concomitant administration of neomycin may lead to an enhanced reduction of postprandial blood glucose and to an increase in the frequency and severity of gastrointestinal adverse reactions. If the symptoms are severe, a temporary dose reduction of acarbose may be warranted.

Colestyramine: The concomitant administration of colestyramine may enhance the effects of acarbose, particularly the reduction of postprandial insulin levels. Simultaneous administration of acarbose and colestyramine should, therefore, be avoided. If both acarbose and colestyramine therapy are withdrawn simultaneously, caution should be exercised as a rebound phenomenon has been observed with respect to insulin levels in non-diabetic subjects.

Digoxin: In individual cases, acarbose may affect digoxin bioavailability, which may require dose adjustment of digoxin.

Intestinal Adsorbents: On the basis of general considerations, the simultaneous use of intestinal adsorbents (e.g. charcoal), and digestive enzyme preparations (e.g. amylase, pancreatin) may reduce the effect of acarbose and should not be taken concomitantly and be avoided wherever possible.

Antacids: The concomitant administration of acarbose and antacids does not alter the effect of acarbose. The administration of antacid preparations is unlikely to ameliorate the gastrointestinal symptoms of acarbose and therefore should not be recommended for this purpose.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies in rats after oral administration produced no untoward effect on fertility or on the overall capacity to reproduce at oral dose levels of 540 mg/kg/day (approximately half the exposure at the maximal therapeutic dose based on the AUC in rats).

Use in pregnancy – Pregnancy Category B3

Studies in rats and rabbits have not yielded any evidence of teratogenic or embryotoxic effects due to acarbose when administered at oral doses up to 540 and 480 mg/kg/day, respectively (approximately half the exposure at the maximal therapeutic dose based on the AUC in rats). At oral doses of 480 mg/kg/day, acarbose caused resorptions in rabbits and increased prenatal losses in rats during organogenesis, but was not teratogenic. There are, however, no adequate and well controlled studies in pregnant women.

Acarbose should not be administered during pregnancy as no information from controlled clinical studies is available on its use in pregnant women.

Use in lactation

Acarbose and/or its metabolites are secreted into milk in rats, with milk levels reaching ten times the maternal plasma levels. No information is available on the concentrations of acarbose or its metabolites which may appear in human milk following administration of acarbose. Consequently, acarbose should not be administered to nursing mothers unless the benefit outweighs the possible risk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The majority of adverse experiences reported to acarbose are gastrointestinal, such as flatulence, diarrhoea and abdominal pain, which result from the pharmacodynamic action of the drug. The majority of symptoms are of mild or moderate intensity and are dose-dependent. In studies of ≥6 months duration, the symptoms occurred early (within 1 - 2 months of treatment) and improved tolerability with longer duration of treatment was observed. Failure to adhere to the prescribed diabetic diet, however, can lead to an intensification of these symptoms. Rarely, these gastrointestinal events may be severe and be confused with or due to ileus (see section 4.3 Contraindications). In individual cases hypersensitive skin reactions may occur e.g. erythema, exanthema and urticaria. Rarely, cases of hepatitis and/or jaundice have been reported.

The frequency of adverse drug reactions reported with acarbose 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 = 7,278; status: 10 Feb 2006) are summarized in the table below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to <1/100) and rare (≥ 1/10,000 to < 1/1,000).

System Organ Class (MedDRA)	Very Common >10%	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%
Vascular Disorders				Oedema
Gastrointestinal Disorders	Flatulence	Diarrhoea Gastrointestinal and abdominal pains	Nausea Vomiting Dyspepsia	
Hepatobiliary Disorders			Hepatic enzymes increased	Jaundice

Soft stools are often produced by acarbose, but if the dosage of the individual case is too high, or after simultaneous ingestion of cane sugar, the stools can become unformed or even liquid. Should diarrhoea persist, patients should be closely monitored and the dosage reduced, or therapy withdrawn, if necessary.

In addition events reported as liver disorder, hepatic function abnormal, and liver injury have been received especially from Japan. Five cases of fulminant hepatitis with fatal outcome have been reported in Japan. A relationship to acarbose cannot be excluded.

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.

Post Marketing Adverse Event Reports:

Blood and Lymphatic System Disorders:
Unknown frequency: Thrombocytopenia

Immune System Disorders:
Unknown frequency: Allergic reaction (rash, erythema, exanthema, urticaria)

Gastrointestinal Disorders:
Unknown frequency: Subileus/ileus, Pneumatosis cystoides intestinalis

Hepatobiliary Disorders:
Unknown frequency: Hepatitis

Skin and subcutaneous tissue disorders:
Acute generalised exanthematous pustulosis

Elevated Serum Transaminase Levels: See section 4.4 Special warnings and precautions for use.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosage of acarbose taken with food and/or drinks containing carbohydrates, can result in an exacerbation of the intestinal effects, i.e. diarrhoea, flatulence, and tympanism.

In the event of overdose with acarbose in the absence of food, excessive intestinal effects are not expected to occur. Hypoglycaemia is unlikely to occur.

Carbohydrate containing food and/or drinks should be avoided for 4-6 hours following overdosage with acarbose.

Diarrhoea should be treated by standard conservative measures.

No specific antidotes to acarbose is known.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Acarbose exerts its activity in the intestinal tract. In contrast to sulfonylureas, it has no stimulatory action on the pancreas.

The action of acarbose depends on an inhibition of intestinal enzymes (alpha-glucosidases) involved in the degradation of ingested disaccharides, oligosaccharides, and polysaccharides, but not monosaccharides. Maximal specific inhibitory activity is against sucrase. This leads, dose dependently, to a delayed digestion of the above carbohydrates. The result is that absorbable monosaccharides (dextrose) originating from carbohydrates are released more slowly and hence more slowly taken up into blood. Absorption of monosaccharides is not affected. In this way, acarbose reduces the postprandial rise in blood glucose, the blood-glucose fluctuations in the course of the day become truncated, and the mean blood-glucose level is reduced. Acarbose lowers abnormally high levels of glycosylated haemoglobin.

Clinical trials

Clinical Experience in Non-Insulin Dependent Diabetes Mellitus (NIDDM) Patients on Dietary Treatment Only: Results from six controlled, fixed-dose, monotherapy studies of acarbose in the treatment of NIDDM, involving 769 acarbose-treated patients, were combined and a weighted

average of the difference from placebo in the mean change from baseline in glycosylated haemoglobin (HbA1c) was calculated for each dose level as presented below.

Table 1

Mean change in HbA_{1c} in Fixed-Dose Monotherapy Studies			
Dose of Acarbose*	**N**	**Change in HbA_{1c} %**	**p-Value**
25 mg t.i.d.	110	-0.44	0.0307
50 mg t.i.d.	131	-0.77	0.0001
100 mg t.i.d.	244	-0.74	0.0001
200 mg t.i.d.**	231	-0.86	0.0001
300 mg t.i.d.**	53	-1.00	0.0001

*Acarbose was statistically significantly different from placebo at all doses. Although there were no statistically significant differences among the mean results for doses ranging between 50 to 300 mg t.i.d. some patients may derive benefit by increasing the dosage from 50 to 100 mg t.i.d.
**Although studies utilised a maximum dose of 200 or 300 mg t.i.d. the maximum recommended dose for patients is 200 mg t.i.d.

Clinical Experience in NIDDM Patients Receiving Sulfonylureas: Acarbose was studied as adjunctive therapy to sulfonylurea treatment in two large, placebo-controlled, double-blind, randomised studies of 24 weeks duration, in which 540 patients were included in the efficacy analysis. In addition, acarbose was studied as adjunctive therapy to sulfonylurea treatment in a third study of one year duration, in which patients were stratified according to background therapy. Study 1 (Table 2) involved patients under treatment at entry with diet alone who were subsequently randomised to four treatment groups. At the end of the study, patients in the acarbose + tolbutamide group showed a mean treatment effect on glycosylated haemoglobin (HbA1c) of -1.78% and were receiving a significantly lower mean daily dose of tolbutamide than patients in the tolbutamide-alone group. Also, the efficacy in the acarbose + tolbutamide groups was significantly better than in the other three treatment groups. Study 2 (Table 2) involved patients taking background treatment with maximum daily doses of sulfonylureas. At the end of this study, the mean effect of the addition of acarbose to maximum sulfonylurea therapy was a change in HbA1c of -0.54%. In addition, there was a significantly greater proportion of patients in the acarbose + sulfonylurea group who reduced their sulfonylurea dose as compared to patients in the placebo + sulfonylurea group. In Study 3 (Table 2), the addition of acarbose to a background treatment of sulfonylurea in 96 patients produced an additional change in mean HbA1c of -0.9%.

Table 2

Study	Treatment	HbA_{1c} (%)			p-Value
		Mean Baseline*	Mean Change from Baseline	Treatment Difference** (90% Confidence Interval)	
1	Placebo	9.48	+0.05	-	-
	Acarbose 200† mg t.i.d.	9.19	-0.71	-0.76 (-1.05, -0.47)	0.0005
	Tolbutamide 250-1000 mg t.i.d. (mean dose 2.4 g/d)	9.28	-1.22	-1.27 (-1.56, -0.98)	0.0001
	Acarbose 200† mg t.i.d. + Tolbutamide 250-1000 mg t.i.d. (mean dose 1.9 g/d)	8.99	-1.73	-1.78 (-2.08, -1.48)	0.0001
2	Sulfonylurea + Placebo	9.56	+0.24	-	-
	Sulfonylurea + Acarbose 50-300† mg t.i.d.	9.64	-0.30	-0.54 (-0.83, -0.25)	0.0096
3	Sulfonylurea + Placebo	8.00	+0.10	-	-
	Sulfonylurea + Acarbose 50-200† mg t.i.d.	8.10	-0.80	-0.90 (-1.33, -0.47)	0.0020
	Metformin + Placebo	7.9	+0.3	-	-
	Metformin + Acarbose 50-200† mg t.i.d.	7.8	-0.5	-0.8 (-1.30, -0.30)	0.0106

* Normal range: 4-6%

** The result of subtracting the placebo group average.

† Although studies utilised a maximum dose of 200 or 300 mg t.i.d., the maximum recommended dose for patients is 200 mg t.i.d.

Clinical Experience in NIDDM Patients Receiving Metformin: Acarbose was also studied as adjunctive therapy to metformin treatment in a one year study (Study 3). In this study (Table 2), the addition of acarbose to 74 patients on metformin treatment produced an additional change in mean HbA_{1c} of -0.8%.

As can be seen by the above studies, acarbose lowers HbA_{1c} levels either alone or in combination with other oral hypoglycaemic agents. Overall 58% of the NIDDM patients studied were women. There is no long-term data on morbidity and mortality.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

One to 2% of an oral dose of acarbose is absorbed from the gastrointestinal tract as unchanged drug. After the oral administration of 200 mg ^{14}C-labelled acarbose (200 mg) to 6 healthy volunteers, approximately 35% of total radioactivity (changed and unchanged drug) appeared in the urine. An average of 51% of the oral dose was excreted in the faeces as unabsorbed drug-related radioactivity within 96 hours of ingestion. The proportion of active substance excreted in the urine was 1.7% of

the administered dose. The low systemic bioavailability of the parent drug is therapeutically desired, because acarbose acts locally within the gastrointestinal tract. Following oral dosing with acarbose, peak plasma concentrations of radioactivity were attained 14 - 24 hours after dosing (586.3 ± 282.7 µg/L after 20.7 ± 5.2 hours), while peak plasma concentrations of active drug were attained at approximately 1 hour (52.2 ± 15.7 µg/L after 1.1 ± 0.3 hours). The delayed absorption of acarbose-related radioactivity reflects the absorption of metabolites that may be formed by either intestinal bacteria or intestinal enzymatic hydrolysis.

Metabolism
Acarbose is metabolised exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. A fraction of these metabolites (approximately 34% of the dose) was absorbed and subsequently excreted in the urine. At least 13 metabolites have been separated chromatographically from urine specimens. The major metabolites have been identified as 4-methylpyrogallol derivatives (i.e. sulfate, methyl, and glucuronide conjugates). One metabolite (formed by the cleavage of a glucose molecule from acarbose) also has α-glucosidase inhibitory activity. This metabolite, together with the parent compound, recovered from the urine, accounts for less than 2% of the total administered dose.

Excretion
The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given intravenously, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an oral dose was recovered in the urine as active (i.e. parent compound and active metabolite) drug. This is consistent with the low bioavailability of the parent drug. The plasma elimination half-life of acarbose activity is approximately 2 hours in healthy volunteers. Consequently, drug accumulation does not occur with three times a day (t.i.d.) oral dosing.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Acarbose showed no genotoxic potential in a series of assays for gene mutations, chromosomal damage and DNA damage.

Carcinogenicity
Acarbose increased the incidences of hypernephroid carcinomas and cortical adenomas of the kidneys and Leydig cell tumours in the testes of Sprague-Dawley rats at dietary concentrations of approximately 23 mg/kg/day and under conditions of severe malnutrition developing from glucosidase inhibition (reduced glucose utilisation, loss of isocaloric state).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

In addition to acarbose, ACARBOSE VIATRIS tablets contain the following inactive ingredients: microcrystalline cellulose, pregelatinised maize starch, colloidal anhydrous silica and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

ACARBOSE VIATRIS is available in PVC/PE/PVDC/Al blister packs of 90 tablets.

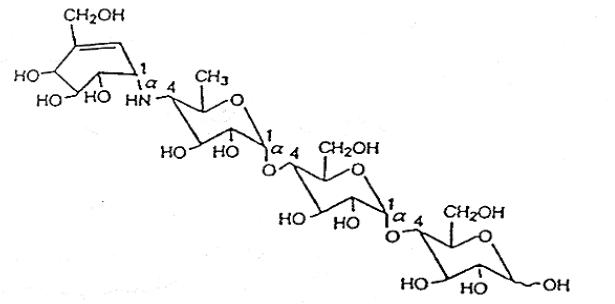
Australian Register of Therapeutic Goods (ARTG)
AUST R 226796 – ACARBOSE VIATRIS acarbose 50 mg tablet blister pack
AUST R 226797 – ACARBOSE VIATRIS acarbose 100 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



ACARBOSE VIATRIS contains acarbose which is a complex oligosaccharide of microbial origin. Acarbose is made up of an unsaturated cyclitol unit, an amino sugar and a maltose residue. Acarbose is a white or yellowish powder with a molecular weight of 645.6. Acarbose is very soluble in water and has a pKa of 5.1. The empirical formula is C25H43NO18

CAS number
56180-94-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4: Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

14 May 2015

10 DATE OF REVISION

13 April 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Addition of following contraindications: - severe hepatic impairment - colonic ulceration - chronic intestinal disease (e.g. Roemhelds syndrome, major hernias, intestinal obstruction and intestinal ulcers) - diabetic ketoacidosis
4.4	Addition of following warnings and precautions: - general: coadministration of antacid preparations - fulminant hepatitis - severe hepatic impairment - use in renal impairment
4.5	Addition of interactions with other medicines (colestyramine).
4.8	Addition of adverse effects - acute generalised exanthematous pustulosis (post-marketing adverse effects).
4.9	Update to overdose section.
Header, 4.8	Minor editorial changes.