acute heart failure, recent myocardial infarction, or shock, may increase the risk of lactic acidosis. Other conditions that may also predispose to lactic acidosis in a patient taking a biguanide include excessive alcohol intake and hepatic impairment. Biguanides should be temporarily stopped for examinations using contrast media (see under Interactions, below).

Insulin is preferred for the treatment of diabetes in pregnancy.

Owing to the possibility of decreased vitamin B_{12} absorption, annual monitoring of vitamin B_{12} concentrations is advisable during long-term treatment.

Driving. In the UK, patients with diabetes mellitus treated with insulin or oral hypoglycaemics are required to notify their condition to the Driver and Vehicle Licensing Agency, who then assess their fitness to drive. Patients treated with oral hypoglycaemics are generally allowed to retain standard driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years. Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur. Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (field of vision of at least 120°) for a licence to be valid. Patients treated with diet or oral hypoglycaemics are normally allowed to hold vocational driving licences for heavy goods vehicles or passenger carrying vehicles; those treated with insulin may not drive such vehicles, and are restricted in driving some other vehicles such as small lorries and minibuses.

References.

1. British Diabetic Association (Diabetes UK). Information sheet: driving and diabetes: May 2008. Available at: http://www.diabetes.org.uk/Documents/catalogue/driving_and_diabetes-may_08.pdf (accessed 20/08/08)
2. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

Interactions

Use of a biguanide with other drugs that lower blood-glucose concentrations increases the risk of hypoglycaemia, while drugs that increase blood glucose may reduce the effect of biguanide therapy.

In general fewer drug interactions have been reported with biguanides than with sulfonylureas. Alcohol may increase the risk of lactic acidosis as well as of hypoglycaemia. Care should be taken if biguanides are given with drugs that may impair renal function.

Anticoagulants. For the effect of metformin on *phenprocoumon* activity, see Antidiabetics, p.1428.

Antivirals. Fatal lactic acidosis has been reported[1] in a patient given metformin with *didanosine*, *stavudine*, and *tenofovir*.

1. Worth L, *et al*. A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Cimetidine. Cimetidine increased plasma-metformin concentrations in 7 healthy subjects.[1] The renal clearance of metformin was reduced; competition for proximal tubular secretion was considered responsible. A reduction in metformin dosage may be required in patients taking metformin and cimetidine, in order to reduce the risk of lactic acidosis.

1. Somogyi A, *et al*. Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; **23:** 545–51.

Contrast media. Biguanides should be temporarily stopped for examinations using iodinated contrast media and withheld after the examination until normal renal function is confirmed, because of the risk of contrast media-induced renal impairment leading to biguanide toxicity and associated lactic acidosis. Licensed product information for some contrast media preparations warns that biguanides should be temporarily stopped 48 hours before the examination, and withheld for at least 48 hours after and until normal renal function is confirmed.

A number of guidelines on the use of iodinated contrast media give advice for the management of patients taking metformin. Some suggest that, in general, metformin can be stopped at the time of the examination.[1,2] Others are more detailed, suggesting that if serum-creatinine is normal metformin may be stopped at the time of the examination, but that if it is raised metformin should be stopped 48 hours before giving the contrast medium.[3,4] They all agree that metformin should be withheld for 48 hours after the examination and until normal renal function is confirmed, although one suggests that no special precaution is needed for patients with normal serum-creatinine who are to be given a low volume of iodinated contrast medium (up to 100 mL).[3]

1. Committee on Drugs and Contrast Media, Commission on General and Pediatric Radiology of the American College of Radiology. Manual on contrast media, 5th ed. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx (accessed 26/06/07)
2. Benko A, *et al*. Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J* 2007; **58:** 79–87. Correction available at: http://www.car.ca/Files%5CNephropathy.pdf (accessed 20/08/08) [correct version]
3. Board of the Faculty of Clinical Radiology; The Royal College of Radiologists. Standards for iodinated intravascular contrast agent administration to adult patients (issued November 2005). Available at: http://www.rcr.ac.uk/docs/radiology/pdf/IVcontrastPrintFinal.pdf (accessed 26/06/07)
4. European Society of Urogenital Radiology. ESUR guidelines on contrast media (version 6.0, issued February 2007). Available at: http://www.esur.org/fileadmin/Guidelines/ESUR_2007_Guideline_6_Kern_Ubersicht.pdf (accessed 26/06/07)

Ketotifen. Platelet counts in 10 diabetic patients receiving biguanides fell (markedly in 3 patients) when they were also given ketotifen.[1] Counts returned to normal a few days after the end of ketotifen therapy. However, the investigators did not consider the effect clinically significant.

1. Doleček R. Ketotifen in the treatment of diabetics with various allergic conditions. *Pharmatherapeutica* 1981; **2:** 568–74.

Sulfonylureas. For reference to an apparent increase in mortality with an intensive regimen of metformin plus a sulfonylurea, see p.462.

Uses and Administration

The biguanide antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p.431). They are given to supplement treatment by diet modification when such modification has not proved effective on its own. In addition, because biguanides are not associated with weight gain they are preferred in obese patients. Although sulfonylureas (p.460) may be preferred in non-obese patients, a biguanide is often added or given instead to patients who are not responding to a sulfonylurea.

The mode of action of biguanides is not clear. They do not stimulate insulin release but require that some insulin be present in order to exert their antidiabetic effect. Possible mechanisms of action include delay in the absorption of glucose from the gastrointestinal tract, an increase in insulin sensitivity and glucose uptake into cells, and inhibition of hepatic gluconeogenesis. Biguanides do not usually lower blood-glucose concentrations in non-diabetic subjects.

Hyperlipidaemias. The effect of biguanides on lipid metabolism is unclear, although some studies have shown a beneficial effect on serum-lipid profiles in both obese and lean patients with type 2 diabetes, hypertension, and/or hyperlipidaemia.[1] Reductions in concentrations of total cholesterol, low-density and very low-density-lipoprotein cholesterol have been reported, as well as modest increases in high-density-lipoprotein cholesterol. Some studies have also reported a reduction in serum-triglyceride levels. Such effects may be beneficial in the long-term treatment of type 2 diabetes mellitus with concomitant lipid disorders.

1. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; **49:** 721–49.

Polycystic ovary syndrome. For discussion of the potential of metformin in polycystic ovary syndrome, see p.454.

Preparations

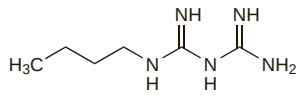
Proprietary Preparations (details are given in Part 3)
Mex.: Azucaps†.
Multi-ingredient: ***Mex.:*** Glinorboral.

Buformin *(USAN, pINN)*

Buformina; Buformine; Buforminum; DBV; W-37. 1-Butylbiguanide.

Буформин

$C_6H_{15}N_5$ = 157.2.
CAS — 692-13-7 (buformin); 1190-53-0 (buformin hydrochloride).
ATC — A10BA03.
ATC Vet — QA10BA03.



Profile

Buformin is a biguanide antidiabetic (p.437). It has been given orally in the treatment of type 2 diabetes mellitus (p.431) in doses of up to 300 mg daily. Buformin is also used as the hydrochloride.

Preparations

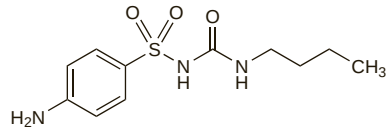
Proprietary Preparations (details are given in Part 3)
Cz.: Adebit†; Silubin†; ***Hung.:*** Adebit; ***Spain:*** Silubin†; ***Switz.:*** Silubin†.

Carbutamide *(BAN, rINN)*

BZ-55; Ca-1022; Carbutamida; Carbutamidum; Glybutamide; Karbutamid; Karbutamidi; U-6987. 1-Butyl-3-sulphanilylurea.

Карбутамид

$C_{11}H_{17}N_3O_3S$ = 271.3.
CAS — 339-43-5.
ATC — A10BB06.
ATC Vet — QA10BB06.



Profile

Carbutamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) in single daily doses of 0.5 to 1 g, but is more toxic than chlorpropamide.

Preparations

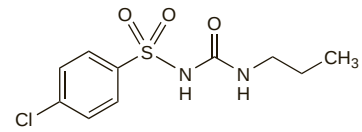
Proprietary Preparations (details are given in Part 3)
Fr.: Glucidoral.

Chlorpropamide *(BAN, rINN)*

Chloropropamid; Chlorpropamid; Chlorpropamidas; Chlorrpropamidum; Clorpropamida; Klooripropamidi; Klórpropamid; Klorpropamid. 1-(4-Chlorobenzenesulphonyl)-3-propylurea.

Хлорпропамид

$C_{10}H_{13}ClN_2O_3S$ = 276.7.
CAS — 94-20-2.
ATC — A10BB02.
ATC Vet — QA10BB02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Chlorpropamide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.
USP 31 (Chlorpropamide). A white crystalline powder having a slight odour. Practically insoluble in water; soluble in alcohol; sparingly soluble in chloroform.

Adverse Effects and Treatment

As for sulfonylureas in general, p.460.

Chlorpropamide may be more likely than other sulfonylureas to induce a syndrome of inappropriate secretion of antidiuretic hormone characterised by water retention, hyponatraemia, and CNS effects. Patients receiving chlorpropamide may develop facial flushing after drinking alcohol.

Precautions

As for sulfonylureas in general, p.461.

Chlorpropamide should be avoided in the elderly and in renal or hepatic impairment because its long half-life increases the risk of hypoglycaemia. The antidiuretic effect of chlorpropamide may cause problems in patients with conditions associated with fluid retention.

Fasting. For the view that although some sulfonylurea antidiabetics may be able to be used with caution in fasting Muslim patients during Ramadan, chlorpropamide is contra-indicated, see under Precautions of Insulin, p.448.

Porphyria. Chlorpropamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Thyroid disorders. Some manufacturers recommend that chlorpropamide should not be used in patients with impaired thyroid function, but see under Sulfonylureas, p.461.

Interactions

As for sulfonylureas in general, p.461.

Chlorpropamide may produce profound facial flushing associated with alcohol ingestion.

Pharmacokinetics

Chlorpropamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. The half-life is about 35 hours. About 80% of a dose is metabolised in the liver; metabolites and unchanged drug are excreted in the urine. Chlorpropamide crosses the placenta and has been detected in breast milk.

Uses and Administration

Chlorpropamide is a sulfonylurea antidiabetic (p.460). It has a duration of action of at least 24 hours, and is given orally in the treatment of type 2 **diabetes mellitus** (p.431) in an initial daily dose of 250 mg as a single dose with breakfast. After 5 to 7 days the dose may be adjusted, in steps of 50 to 125 mg at intervals of 3 to 5 days, to achieve an optimum maintenance dose which is usually in the range 100 to 500 mg daily. Increasing the dose above 500 mg daily is unlikely to produce further benefit, and doses above 750 mg daily should be avoided. Although a reduced dose range has been proposed for the elderly, use of chlorpropamide is inadvisable in this group.

Chlorpropamide, though not the other sulfonylureas, is also sometimes used in cranial **diabetes insipidus** (p.2179). It has been reported to act by sensitising the renal tubules to antidiuretic hormone. The dose has to be carefully adjusted to minimise the risk of hypoglycaemia. An initial dose of 100 mg daily, adjusted if necessary to a maximum of 350 mg daily has been recommended, although doses of up to 500 mg daily have been used.

Diabetes mellitus. Patients with type 2 diabetes whose blood glucose is adequately controlled at first by sulfonylureas often eventually have treatment failure and loss of diabetic control. Results from the UK Prospective Diabetes Study[1] have suggested that the 6-year failure rate was higher in patients treated with glibenclamide (48%) than in those given chlorpropamide (40%). This difference was equivalent to delaying the requirement for additional therapy for a year in chlorpropamide-treated patients.

1. Matthews DR, *et al.* UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. *Diabet Med* 1998; **15:** 297–303.

Preparations

BP 2008: Chlorpropamide Tablets;
USP 31: Chlorpropamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Diabinese; Idle†; Trane; ***Belg.:*** Diabinese†; ***Braz.:*** Clorpromini†; Clorzin†; Diabecontrol; Diabinese; Glicoben; Glicorp; Pramidalin; ***Canad.:*** Novo-Propamide; ***Chile:*** Diabinese; ***Gr.:*** Diabinese; ***Hong Kong:*** Diabinese; ***India:*** Copamide†; ***Indon.:*** Diabinese; ***Israel:*** Diabinese†; Diabitex; ***Ital.:*** Diabemide; ***Malaysia:*** Anti-D†; Diabinese†; Propamide; ***Mex.:*** Aposprod; Diabiclor; Diabinese; Insogen; ***Philipp.:*** Diabinese; ***S.Afr.:*** Diabinese; Hypomide; ***Singapore:*** Anti-D; Chlomide†; Diabinese†; Propamide; ***Spain:*** Diabinese; ***Thai.:*** Diabeedol; Diabinese; Dibecon; Glycemin; Propamide; ***Turk.:*** Diabinese; ***USA:*** Diabinese; ***Venez.:*** Dabinese.

Multi-ingredient: ***India:*** Chlorformin†; ***Ital.:*** Bidiabe; Pleiamide; ***Mex.:*** Insogen Plus; Mellitron; Obinese; ***Switz.:*** Diabiformine.

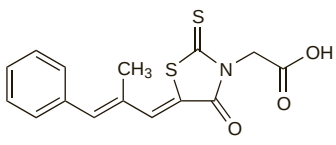
Epalrestat *(rINN)*

Épalrestat; Epalrestatum; ONO-2235. 5-[(*Z*,*E*)-β-Methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid.

Эпалрестат

$C_{15}H_{13}NO_3S_2$ = 319.4.

CAS — 82159-09-9.



Profile

Epalrestat inhibits the enzyme aldose reductase which catalyses the conversion of glucose to sorbitol. It has been suggested that accumulation of sorbitol in certain cells, occurring only in conditions of hyperglycaemia and resulting in a hyperosmotic effect, may be involved in the pathogenesis of some diabetic complications. Aldose reductase inhibitors have no influence on blood-glucose concentrations. Epalrestat is given orally for the treatment of diabetic complications including neuropathy (p.433), in a usual dose of 50 mg three times daily before meals.

◊ References.

1. Goto Y, *et al.* A placebo-controlled double-blind study of epalrestat (ONO-2235) in patients with diabetic neuropathy. *Diabet Med* 1993; **10** (suppl 2): 39S–43S.
2. Uchida K, *et al.* Effect of 24 weeks of treatment with epalrestat, an aldose reductase inhibitor, on peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *Clin Ther* 1995; **17:** 460–6.
3. Hotta N, *et al.* Clinical investigation of epalrestat, an aldose reductase inhibitor, on diabetic neuropathy in Japan: multicenter study. *J Diabetes Complications* 1996; **10:** 168–72.
4. Ikeda T, *et al.* Long-term effect of epalrestat on cardiac autonomic neuropathy in subjects with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 1999; **43:** 193–8.
5. Iso K, *et al.* Long-term effect of epalrestat, an aldose reductase inhibitor, on the development of incipient diabetic nephropathy in type 2 diabetic patients. *J Diabetes Complications* 2001; **15:** 241–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Kinedak.

Exenatide *(BAN, USAN, rINN)*

AC-2993; AC-002993; AC-2993A; Exenatida; Exénatide; Exenatidum; LY-2148568; Synthetic Exendin-4.

Эксенатид

$C_{184}H_{282}N_{50}O_{60}S$ = 4186.6.

CAS — 141758-74-9 (exenatide); 141732-76-5 (exendin-4).

ATC — A10BX04.

ATC Vet — QA10BX04.

H–His–Gly–Glu–Gly–Thr–Phe–Thr–Ser–Asp–Leu–
10
Ser–Lys–Gln–Met–Glu–Glu–Glu–Ala–Val–Arg–
20
Leu–Phe–Ile–Glu–Trp–Leu–Lys–Asn–Gly–Gly–
30
Pro–Ser–Ser–Gly–Ala–Pro–Pro–Pro–Ser–NH_2
39

Adverse Effects and Precautions

Hypoglycaemia can occur in patients given exenatide, particularly when given with a sulfonylurea (see also Interactions, below). Exenatide commonly causes mild to moderate nausea, which is dose-dependent and tends to decrease with continued therapy in most patients. Other adverse effects include vomiting, diarrhoea, nervousness, dizziness, headache, and dyspepsia. Less frequent reports include asthenia, decreased appetite, gastro-oesophageal reflux, and hyperhidrosis. Rashes and hypersensitivity reactions have occurred rarely. Acute pancreatitis has been reported, and in such cases exenatide should be stopped permanently.

Exenatide should not be used in type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Use is not recommended in patients with severe renal impairment, in whom clearance is reduced and adverse gastrointestinal effects have been reported.

Effects on the pancreas. A 69-year-old man developed pancreatitis within a few days of starting exenatide therapy. Serum-lipase concentrations returned to normal and abdominal pain resolved rapidly when exenatide was stopped.[1] The FDA has also reviewed 30 reports of acute pancreatitis in patients treated with exenatide.[2] In 27 cases there was at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridaemia, and alcohol use. Improvement after stopping exenatide was confirmed in 22 reports, and in 3 cases of rechallenge there was a return of symptoms of acute pancreatitis. The FDA subsequently reported[3] in August 2008 that they had received reports of 6 cases of haemorrhagic or necrotising pancreatitis associated with exenatide; all patients required hospitalisation and 2 died. It was recommended that exenatide therapy should be stopped if signs or symptoms of pancreatitis develop and should not be restarted if pancreatitis is confirmed. Other antidiabetic drugs should be considered for those with a history of pancreatitis.

1. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. *Diabetes Care* 2006; **29:** 471.
2. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued October 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatideHCP.htm (accessed 17/10/07)
3. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued August 2008). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatide2008HCP.htm (accessed 20/08/08)

Interactions

A reduction in the sulfonylurea dose may be required when exenatide is added to therapy, because of an increased risk of hypoglycaemia with this combination. No increase in hypoglycaemia occurs when exenatide is used with metformin or a thiazolidinedione. The extent and rate of absorption of oral drugs may be reduced by exenatide. Where such an interaction would be undesirable, the oral medication should be given at least 1 hour before exenatide. If the oral medication is to be taken with food, where possible, it should be with a meal or snack when exenatide is not used.

Pharmacokinetics

After subcutaneous injection, peak plasma concentrations of exenatide are reached in about 2 hours. It is eliminated through the kidneys by glomerular filtration followed by proteolytic degradation, with a terminal half-life of about 2.4 hours. Clearance is reduced in patients receiving dialysis for end-stage renal disease.

◊ References.

1. Kolterman OG, *et al.* Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2005; **62:** 173–81.
2. Linnebjerg H, *et al.* Effect of renal impairment on the pharmacokinetics of exenatide. *Br J Clin Pharmacol* 2007; **64:** 317–27.

Uses and Administration

Exenatide is a synthetic form of exendin-4, a 39-amino acid peptide isolated from the venom of the Gila monster lizard (*Heloderma suspectum*, Helodermatidae). The drug is an incretin mimic that acts as an agonist at the glucagon-like peptide 1 receptor to enhance insulin secretion in the presence of raised glucose concentrations; it also suppresses inappropriate glucagon secretion and slows gastric emptying. Exenatide is used as adjunctive therapy in type 2 diabetes mellitus (p.431) in patients who do not have adequate glycaemic control with metformin, a sulfonylurea, a thiazolidinedione, or dual therapy with metformin plus a sulfonylurea or thiazolidinedione. It is given by subcutaneous injection in an initial dose of 5 micrograms twice daily within 60 minutes before the morning and evening meals. The dose of exenatide may be increased after 1 month to 10 micrograms twice daily if required.

◊ References.

1. Fineman MS, *et al.* Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes. *Diabetes Metab Res Rev* 2004; **20:** 411–17.
2. Buse JB, *et al.* Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; **27:** 2628–35.
3. Kendall DM, *et al.* Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005; **28:** 1083–91.
4. DeFronzo RA, *et al.* Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 1092–1100.
5. Heine RJ, *et al.* Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; **143:** 559–69.
6. Yoo BK, *et al.* Exenatide: a new option for the treatment of type 2 diabetes. *Ann Pharmacother* 2006; **40:** 1777–84.
7. Ratner RE, *et al.* Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2006; **8:** 419–28.
8. Nauck MA, *et al.* A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 2007; **50:** 259–67.
9. Zinman B, *et al.* The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2007; **146:** 477–85. Correction. *ibid.*; 896.
10. Cvetković RS, Plosker GL. Exenatide: a review of its use in patients with type 2 diabetes mellitus (as an adjunct to metformin and/or a sulfonylurea). *Drugs* 2007; **67:** 935–54.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Byetta; ***Austral.:*** Byetta; ***Braz.:*** Byetta; ***Cz.:*** Byetta; ***Port.:*** Byetta; ***UK:*** Byetta; ***USA:*** Byetta.