Chapter 5

ENDOCRINE SYSTEM

5.1 THYROID HORMONES AND ANTITHYROID DRUGS

5.1.1 THYROID HORMONES

Thyroid hormones are secreted from Thyroid Glands. They are thyroxine (T_4) and tri-iodothyronine (T_3). They are also produced synthetically. These include levothyronine and liothyronine. The principal effect of thyroid hormones is to increase the cellular metabolic rate in general and thus to increase the basal metabolic rate (BMR). They also exert a cardio-stimulatory effect which may be the result of direct action on the heart.

Deficiency of thyroid hormones leads to a generalized slowing down of metabolic processes. Infantile/congenital and childhood hypothyroidism affects growth and development, producing serious permanent consequences including mental retardation. Severe cases are short with very low IQ called cretinism. Myxedema in adult slows down

metabolism leading to deposits of glycosamino glycans in intercellular spaces particularly in skin and muscle; severe cases called myxedema .

Thyroid hormones are used mostly replacement therapy in hypothyroidism; and in non-toxic goitre, Hashimoto's Thyroiditis, thyroid nodule and thyroid carcinoma.

Thyroxine sodium (Levothyroxine sodium) is the treatment of choice for replacement therapy.

Starting dose should be low such as 25 micrograms once daily preferably in empty stomach for about a week then titrate the dose so that serum FT4 value become near to the median of the laboratory reference range by next couple of weeks. Once the desire dose is attained monitoring should be carried out at regular interval eg; once in every 3 months; to adjust the dose if required.

Note. Initial dose should not exceed 100 micrograms daily, preferably in empty stomach before breakfast.

In elderly patients or patient with Ischemic heart disease the dose titration should be slower eg; increased dose by 25–50 micrograms at intervals of 4 weeks.

In infants, a daily dose of 10 micrograms/kg up to maximum of 50 micrograms should be given; subsequent doses should be based on serum hormone level plus clinical assessment of growth and development.

Liothyronine sodium has a similar action to thyroxine but is more potent; 20 micrograms of it is equivalent to 100 micrograms of thyroxine. Its effect develops after a few hours and disappears within 24 to 48 hours of discontinuation. It may be used in severe hypothyroid states where a rapid response in needed. Liothyronine by intravenous injection is the treatment of choice in myxedema / hypothyroid coma, which is a medical emergency arising as an ultimate stage of severe long-standing untreated hypothyroidism.

In primary hypothyroidism, serum FT_4 and FT_3 levels are low coupled with high TSH level; but in secondary or tertiary hypothyroidism, TSH level is low or normal. The aim of thyroid replacement therapy is to maintain the FT4 level at or slightly above the median of the reference range which should keep TSH in primary hypothyroidism within its normal range. Monitoring has to be done clinically as well as biochemically. Patients should be informed that thyroid replacement therapy is for life long.

THYROXINE SODIUM [ED]

(Other names: Levothyroxine sodium; L-Thyroxine sodium)

Indication: hypothyroidism

Cautions: panhypopituitarism or predisposition to adrenal insufficiency from any cause (initiate corticosteroid therapy before statring thyroxine); elderly, cardiac ischaemia, ECG evidence of myocardial infarction, diabetes insipidus, diabetes mellitus (increase dose may be needed for antidiabetic drugs including insulin)

Interactions*: see Appendix-2*

Initial dosage: a pre-therapy ECG is valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia. Too rapid increase in dosage may increase metabolism that can cause vomiting, diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain; if such symptoms appear, reduce dose or withhold for 1-2 days before starting again at a lower dosage

Contraindication: thyrotoxicosis

Side-effects: usually at excess dosage *(see Initial dosage)*, there may be anginal pain, cardiac arrhythmias, hyperactivity, mood swings, palpitations, skeletal muscle cramps, tachycardia, diarrhoea, vomiting, tremors, restlessness, insomnia, headache, flushing, sweating and rapid weight loss

Dose: ADULTS, initially with a low dose of 25- 50 micrograms once daily orally in

empty stomach and regular increment to a dose that keeps FT_4 at or near to the middle of the normal range and which also will keep TSH within normal range. Monitoring is done clinically as well as biochemically

CHILD, in congenital hypothyroidism, start with 25 microgram daily and increase the dose by 25 micrograms every 2–4 weeks until mild hyperthyroidism symptoms appear; then reduce the dose slightly so that serum FT_4 is near upper limit of normal; in children above 1 year of age, start with 2.5 – 5 micro-grams/kg daily and then increase the dose stepwise to attain serum FT_4 at near upper limit of the normal

Proprietary Preparations

Eltroxin (I)*(GSK),* Tab., 50 microgram, Tk. 2.56/Tab.
Euthycin *(Incepta),* Tab., 50 microgram, Tk. 1.20/Tab.
Leroxin *(Popular),* Tab., 50 microgram, Tk. 1.20/Tab.
Thynor *(Eskayef),* Tab., 50 microgram, Tk.1.50/Tab.
Thyrin *(Square),* Tab., 25 microgram, Tk.1.10/Tab.; 50 microgram, Tk.1.60/Tab.
Thyrolar *(Acme),* Tab., 25 microgram, Tk. 0.70/Tab.; 50 microgram, Tk. 1.20/Tab.
Thyrotab *(Ibn Sina),* Tab., 50 microgram, Tk. 2.00/Tab.
Thyrox *(Renata),* Tab., 50 microgram, Tk. 1.60/Tab.
Tyroid *(ACI),* Tab., 50 microgram, Tk. 1.35/Tab.

5.1.2 ANTITHYROID DRUGS

Antithyroid drugs are used in the treatment for hyperthyroidism where there high uptake iodine by the thyroid example Graves' disease, mutinodular toxic goter and toxic thyroid nodule. Hyperthyroidism is defined as a clinical syndrome consisting of symptoms and signs reflecting peripheral response to excessive amount of thyroid hormone. Clinical manifestations of hyperthyroidism (thyrotoxicosis) include restlessness, tachycardia, weight loss, tremulousness etc. In hyperthyroidism, biochemically, there is TSH suppression along with rise of free T_3 and free T_4 levels. There are three modalities for the treatment of hyperthyroidism: Antithyroid drugs, radioablation and surgery.

In Graves disease antithyroid drugs are used for controlling hyperthyroidism until the disease under-goes spontaneous remission. In multinodular toxic goiter it is use alone or for preoperative preparation and in toxic thyroid nodule anti thyroid drug is alone or prior to radioablesion. They are usually well tolerated with mild leukopenia or rashes developing in a few percent of cases, usually during the first 6-8 weeks of therapy. During this time, the blood count should be checked every 2 weeks or if a sore throat or other signs of infection develop. These drugs are generally given in high doses initially, then be gradually reduced to a maintenance dose which is continued for 12-18 months. If surgery (partial thyroidectomy) is needed, then iodine should be given for 10-14 days to reduce vascularity of thyroid glands. **Carbimazole** is the most commonly used antithyroid drug. It is given in a daily dose of 15–30 mg and maintained at this dose until the patient become euthyroid, usually after 4-8 weeks; the dose is than gradually reduced to maintenance of between 5–15 mg daily; therapy is usually given for 18 months. CHILD may be given an initial dose of 15 mg daily, and then adjusted according to response. Puritius and rashes are common and can be treated with antihistamines without discontinuing therapy. Patients should be advised to report any sore throat immediately because of the rare but possible complication of agranulocytosis; for the same reason, routine blood counts during the course of therapy is also recommended. If side effects of **carbimazole** are severe, propylthiouracil may be substituted. **Propylthiouracil** is given in a daily dose of 300 to 600 mg and maintained on this dose until the patient become euthyroid; the dose may then be progressively reduced to a maintenance level of between 50–150 mg daily.

Antiparathyroid drug, Paricalcitol is used for the prevention and treatment of secondary hyperparathyroidism

Iodine may be given in the form of Aqueous Iodine Oral Solution (Lugol's Iodine) for 10-14 days in addition to **carbamizole** or **propylthiouracil** prior to partial thyroidectomy to assist control and reduce vascularity of the thyroid. Iodine should not be used for long-term treatment since its antithyroid action tends to diminish with time. Although antithyroid drugs have a short half-life they need only be given once daily because of their prolonged effect on the thyroid. Over-treatment may lead to a rapid onset of hypothyroidism, and this should be avoided particularly during pregnancy since it can cause fetal goitre.

Radioablation of the thyroid gland is used in thyrotoxicosis when antithyroid drugs fail to produce desired results. Radioablation may cure hyperthyroidism due to a single hyperfunctiong nodule or control hyperthyroidism with multiple nodules. Radioactive sodium iodide solution is used for treatment of thyrotoxicosis at all ages, particularly when medical therapy or compliance is a problem, in patient with cardiac disease, and in cases of relapse after thyroidectomy.

Propranolol (a beta-blocker) is useful for rapid relief of thyrotoxic symptoms and may be used as short term adjunct to antithyroid drugs or radioactive iodine to control severe sympathetic over-activity, such as in thyroid storm (see below). Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventicular arrhythmias due to hyperthyroidism. Propranolol may be used in conjunction with iodine to prepare mild thyrotoxic patients for surgery. Laboratory thyroid function tests are not altered by beta-blockers. Use of beta blockers in mild to moderate hyperthyroidism is unnecessary.

Most cases of thyrotoxicosis do not require surgery. However, hyperfunctioning multinodular goiter requires debulking surgery if antithyroid drugs or radioablation fails to control. Patients must be informed that after surgery, follow up is needed for life long.

Thyrotoxic crisis ('thyroid storm') is a medical emergency arising out of an extreme accentuation of thyrotoxicosis. It is usually associated with toxic multinodular goitre or subtotal thyroidectomy, surgical cases inadequately prepared before the operation. Other precipitating factors are radiation thyroiditis, diabetic ketoacidosis, toxemia of pregnancy and parturition. Management of the crisis requires emergency treatment with intravenous fluids, propranolol (5mg) and hydrocortisone (100 mg every 6 hours, as sodium succinate), as well as oral iodine solution and carbimazole or propylthiouracil, which may need to be administrated by nasogastric tube.

Pregnancy and breast-feeding: Radioactive iodine therapy is contra-indicated during pregnancy. Propyl-thiouracil or carbimazole can be given, but the blocking-replacement regimen (see notes above) is not suitable. Both propylthiouracil and carbimazole cross the placenta and in high dose can cause foetal goitre and hypothyroidism; the lowest dose that control the hyperthyroid state should be used (requirements of antithyroid drugs tend to fall during pregnancy). Rarely carbimazole has been associated with aplasia cutis of neonate. Carbimazole and propylthio-uracil appear in the breast milk but this dose not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used.

CARBIMAZOLE

Indications: hyperthyroidism

Cautions: large goiter, liver disorders, pregnancy, breast-feeding *(see also Appendix-6)*

Side-effects: nausea, rashes, headache, pruritus, mild gastrointestinal dis-turbances, arthalgia; agranulocytosis; rarely alopecia, jaundice

WARNING. A white blood cell count should be performed if there is any clinical evidence of infection, especially sore throat. Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

Dose: *see notes above*

COUNSELING: warn patient to report immediately if sore throat, mouth ulcers, fever, malaise, or non-specific illness develops. Recommend routine blood counts from time to time during therapy

Proprietary Preparations
Carbizol *(Square),* Tab. 5 mg, Tk. 3.01/Tab.
Carbiroid *(White Horse),* Tab. 5 mg, Tk. 4.80/Tab.

IODINE AND IODIDE PREPRATION

Indications: thyrotoxicosis (preoperative)

Cautions: pregnancy, children (not for long-term treatment)

Contraindications: breast-feeding

Side-effects: hypersensitivity reactions including headache, laryngitis, lachry-mation, conjuctivities, coryzalike symptoms, pain in the salivary glands, rashes; on prolong treatment depression, insomnia, impotence, may occur; goitre in infants of mothers taking iodides

COUNSELING: warn patient to report immediately if sore throat, mouth ulcers, rashes, fever, malaise, or non-specific illness develops

Generic Preparation: Aqueous Iodine Oral solution (Lugol's Solution), iodine 5%, potassium iodide 10% in purified water, freshly boiled and cooled; total iodine 130 mg/ml

Dose: 0.1–0.3 ml, 3 times daily well diluted with milk or water

5.2 DRUGS USED IN DIABETES

5.2.1 INSULINS
5.2.1.1 SHORT ACTING INSULIN.
5.2.1.1.1 INTERMEDIATE AND LONG ACTING INSULIN
5.2.2 ORAL HYPOGLYCEMIC AGENTS (OHA)
5.2.2.1 SULPHONYLUREAS
5.2.2.2 BIGUANIDES
5.2.2.2.1 OTHER ORAL ANTI-DIABETIC DRUGS.
5.2.3 DIABETIC EMERGENCY
5.2.3.1 DIABETIC KETOACIDOSIS (DKA)
5.2.3.2 HYPOGLYCEMIA
5.2.4 DRUGS USED IN DIABETIC NEPHROPATHY

5.2 DRUGS USED IN DIABETES

Diabetes mellitus (DM) is a metabolic disorder caused by a deficiency of insulin in the body or resistance to the action of insulin if the pancreas is producing it. It is characterized by hyperglycaemia (high blood glucose) and disturbances of carbohydrate, fat and protein metabolism. There are 4 principal types of diabetes: Type-I, type-2, Gestational and Secondary diabetes.
Type-1 DM is due to deficiency of insulin following autoimmune destruction of pancreatic beta cells; patients with this type of diabetes require insulin for survival. Type-2 DM is due to reduced secretion of insulin or to peripheral resistance to its action. It is also referred to as non-insulin dependent diabetes mellitus (NIDDM)). Type-2 DM may be controlled on diet alone but many of them require oral hypoglycemic agents (OHA) or insulin for satisfactory control. Secondary diabetes has obvious genetic or environmental factors and Gestational diabetes is diabetes that identified during pregnancy. Diagnosis of diabetes (and categories of glucose intolerances – IGT & IFG) is classically made by oral glucose tolerance test.

ORAL GLUCOSE TOLERANCE TEST (OGTT): The test should be done in morning after 10-16 hours overnight fasting. The person should take at least previous 3 days unrestricted diet containing more than 150 g carbohydrates daily. A fasting blood sample is collected. Then an oral glucose load (for adult 75 g, for child

1.75 g/kg body weight up to maximum 75 g) is given in 250-300 ml of water over the course of 5 minutes. A blood sample is collected 2 hours after the test load. If glucose is not estimated immediately, the blood sample may be preserved with sodium fluoride (6 mg/ml whole blood) centrifuged and plasma frozen until estimation. Smoking, tea or physical stress is not allowed during the test. Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia are tabled as follows:

Table 5.2 A. Diagnostic values for the oral glucose tolerance test (Glucose concentration mmol/L)

		Capillary Whole Blood	**Venous Plasma**
DM	Fasting 2-hrs after glucose load	=/> 6.1 =/> 11.1	=/> 7.0 =/> 11.1
IGT	Fasting 2-hrs after glucose load	<6.1 and =/> 7.8	<6.1 and =/> 7.8 to <11.1
IFG	Fasting 2-hrs after glucose load	6.1 to 6.9 and < 7.8	6.1 to 6.9 and < 7.8
Normal	Fasting 2-hrs after glucose load	<6.1 and < 7.8	<6.1 and =/> 7.8

MONITORING OF THERAPY

Monitoring of therapy is an integral part of management. Monitoring of blood glucose has generally superseded detection of urinary glucose. For adequate diabetic control the aim is to reduce fasting plasma glucose to below 5.6mmol/L and post prandial concentration below 10 mmol/L.

Measurement of total glycated or glycolsylated haemoglobin (HbA_{1c}) provides a good indication for long term control of blood sugar. The ideal HbA_{1c} level is around 7%, which is often difficult to achieve without risk of hypoglycemia (Table 5.2B).

The value of self-monitoring of blood glucose in Type-2 diabetes is debatable and may be necessary for intensified insulin regimens, when tight control is required.

Table 5.2 B: Diagnostic values of HbA1c for diabetes

HbA1c (%)	**Normal/Abnormal**
4- 6.5	Normal for those without diabetes
6.5 – 7.5	Target ranges for those with diabetes
8.0 – 9.5	High diabetes
> 9.5	Very high diabetes

DIABETES AND PREGNANCY

Adverse pregnancy outcomes like abortions and congenital malformations are more common in diabetics; improved management of diabetes particularly early in pregnancy lessens the incidence of such events.

Insulin is the preferred treatment in pregnancy even in Type-2 diabetes; patients on OHA should be switched to insulin. Insulin requirement may decrease in first trimester but then increases during later two, reaching about thrice pre-pregnancy requirement at term, then they decline once labour has begun and fall again after delivery. Pregnant diabetics are at risk of nocturnal hypoglycaemia due to continued foetal glucose consumption. They are prone to develop ketoacidosis, which need to be treated with urgency.

Diabetes which develops during pregnancy (gestational diabetes) may simply be IGT and can be managed by diet alone or if necessary also with insulin.

DIABETES AND SURGERY

If blood glucose is not properly controlled, the outcome of surgery can be poor; there is chance of wound infection and delayed healing. Insulin is suitable for the treatment of diabetic

patients during the perioperative period. There is debate, however, about the optimum route of insulin administration during surgeries. Although some clinicians advocate subcutaneous insulin administration; most of them now recommend intravenous insulin infusion. Most physicians give patients half of their normal dose of insulin as intermediate acting insulin subcutaneously on the morning before an operation, and then administer soluble insulin 16 units/litre added to the intravenous infusion of 5% dextrose containing potassium chloride 10 mmol/litre (provided the patient is not hyperkalaemic), and the infusion is run to adjust the insulin dose. Blood-glucose concentration should be measured preoperatively and then every 2 hours.

5.2.1 INSULIN [ED]

Insulin is a polypeptide hormone of complex structure, secreted by the beta cells of the pancreas. It plays key roles in the metabolism of carbohydrates, fats and proteins. There are differences in the amino acid sequences of animal and human insulin. Formerly, the source of commercially available insulin was from the pancreas of cows or pigs. Now a days recombinant DNA technology (using *E. coli* bacteria) is the main source of biosynthetic human insulin. However, there is still a lot of bovine and porcine insulins, as well as natural or enzymatically modified semisynthetic human analogue insulin in the market. Animal and semisynthetic insulins are to a greater or lesser extent immunogenic to man but resistance to insulin action is uncommon.

Insulin is needed by all patients of Type-1 DM regardless of age, those with ketoacidosis, and most of those with rapid onset of symptoms or weight loss. Almost all children with diabetes require it. Type-2 DM cases where other methods fail or with frequent acute infection, tuberculosis, hepatitis, during surgery and with other complications like nephropathy and retinopathy also need insulin. It is also indispensable in acute metabolic decompensated states in Type-2 DM (like diabetic ketoacidosis, hyperosmolar nonketotic coma, lactic acidosis, etc.). Insulin in Type-2 DM is also used as a combination therapy with OHA. The subcutaneous route is ideal in most cases. The dose of insulin is adjusted on an individual basis, by gradually increasing the dose but carefully avoiding hypoglycemic reactions. Based on the onset and duration of action, insulin preparations are of various types. **Short-acting insulins** (e.g. soluble insulin; insulin lispro) have relatively rapid onset of action (about 30-60 minutes) and duration of action up to 8 hours (peak 2-4 hours). Human insulin has a faster onset and shorter duration of action. With insulin lispro (a human insulin analogue), fasting and preprandial blood glucose is a little lower and hypoglycemia occur less frequently. By the intravenous route, only the soluble insulin can be used, not the other types. **Intermediate-acting insulin** (e.g. isophane insulin and insulin zinc suspension) have duration of action of about 24 hours. **Long-acting insulin** (e.g. crystalline insulin zinc suspension) has long duration of action about 28 hours and slower onset of action after about 4 hours.

Biphasic or Premixed insulin contains a combination of a short acting and intermediate-acting insulin in a standard proportion. Side effects of insulin therapy include hypoglycemia, allergy, immunologic reaction, insulin edema and lipodystrophy. Patient should be shown the bottle and explained about the type and source of insulin to ensure that the version dispensed is actually the one the patient was expecting.

EXAMPLES OF INSULIN REGIMENS

An appropriate regimen of insulin therapy must be individualized. Usual regimens are one injection a day, two injections a day, multiple (3 to 7) injections a day and insulin pump.

One injection a day: One injection of intermediate or long acting insulin is

given either in morning or evening pre-meal time. It serves, as supplement/basal secretion. It may be effective in Type-2 DM as monotherapy or in combination with other oral hypoglycemic agents (OHA).

Two injections a day: This is the most commonly used regimen. It can be used in type-1 DM and type-2 DM. A short acting and an intermediate acting-insulin are mixed in proportion that is adjusted by trail and injected before breakfast and dinner. Alternatively, each injection can be either intermediate-acting insulin or biphasic insulin.

Multiple injections: As many as 3 to 7 injections per day may be needed where there is difficulty in achieving optimal control with other regimes. A dose of short-acting insulin is given before each meal, an intermediate-acting/ long acting insulin is given before bedtime and sometimes before breakfast as basal dose. This is very flexible and suitable for those who are very active and cannot comply with a rigid meal plan.

Insulin pump: Insulin pumps are available in two forms-open or closed loop (Artificial Pancreas). The open loop system is composed of two parts a battery-operated pump and a computer programmed system for insulin delivery. The closed loop consists of three parts-a battery-operated pump, a computer controlled insulin delivery system and a glucose sensor giving feedback to the computer. These are portable and designed to deliver basal amount of regular insulin throughout the day as well as meal related boluses.

5.2.1.1 SHORT ACTING INSULIN

Soluble insulin is a short acting form of insulin. It is the only form of insulin that can be used subcutaneously intramuscularly, as well as intravenously. For maintenance regimens it is injected subcutaneously 15 to 30 minute prior to a meal. When injected subcutaneously, soluble insulin has a rapid onset of action (after 30-60 minutes), a peak action between 2 and 4 hours, and duration of action up to 8 hours.

Intravenous route is used during diabetic emergencies and also during major surgery. When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.

The human insulin analogue **Insulin lispro, Aspart or Glulisine** has a shorter duration of action than soluble insulin and also rapid onset of action; so subcutaneous injection may be given close to meal.

SOLUBLE INSULIN[ED]

(Other names: Insulin Injection; Neutral Insulin)

Indications: diabetes mellitus, diabetic ketoacidosis

Cautions: *see notes above;* reduce dose in renal impairment

Interactions: *see Appendix-2*

Side effects: *see notes above;* local reactions and fat hypertrophy at injection site; over dose causes hypoglycemia

Dose: *by subcutaneous*, *intramuscular or intravenous injection or intravenous infusion,* according to patient's requirement and response

Proprietary Preparations

Actrapid *(Novo Nordisk),* Inj., 40 IU/ml ; Tk.198.36/10mlvial
Actrapid *(Novo Nordisk),* Inj., 100 IU/ml Tk.422.15/10 ml vial vial; Cartridge; Tk.1855/box.
Ansulin R *(Square),* Inj., 100 IU/ml Tk. 422.15/10ml vial;40IU/ml Tk. 198.36/10 ml vial ;Cartidge Tk. 223.79/3 ml cartidge
Diasulin R *(ACI),* Inj.,100 IU/ml vial Tk.422.15/10ml;Inj.,40IU/ml Tk. 198.36/10 ml vial
Humulin-R (I) (*Eli Lilly),* Inj. 100 IU/ml. Tk. 680.00/10 ml vial;Tk.265.00/4ml vial; Cartidge, Tk.,336.00/3ml
Insul R *(Popular)*, Inj.40IU/ml, Tk. 195.00/10 ml vial;Inj.,100IU/ml Tk. 415.00/10 ml vial; Inj., Tk. 220.00/3 ml cartidge
Insulet R *(Aristo),* Inj.,vial100IU/ml Tk. 169.70/4 mlvial ;Tk. 422.00/10 ml;40IU/ml,TK.195.00/10ml

Insuman Rapid (I) *(Aventis),* Inj.vial 100 IU/ml. Tk. 281.7/5ml
Maxsulin R*(Incepta)* Inj. 100 IU/mlTk 415.00/10ml vial; 40IU/mlTK.195.00/10mlvial

INSULIN ASPART, INSULIN GLULISNE, INSULIN LISPRO

(Other name: Recombinant human insulin analogues)

Indication: diabetes mellitus

Cautions: *see under Soluble Insulin;* use in children if benefit as good as with Soluble Insulin

Side effects: *see under Soluble Insulin*

Interactions: *see Appendix-2*

Dose: *by subcutaneous injection* according to the patient's requirement and response

Proprietary Preparations
INSULIN ASPART
NovoRapid Penfill(I) *(Novo Nordisk),* 100 IU/ml, Inj. (Cartridge); TK.3875/pkt.
Novo Rapid FlexPen (I) *(Novo Nordisk),* 100 IU/ml, inj., pre-filled pen; TK.865/pen.
INSULIN GLULISNE
Apidra SoloStar (I) *(Sanofi),* Inj., Tk. 4,673.60/3 ml 5Pens ; Inj., Tk. 1,990.28/10 ml vial
INSULIN LISPRO
Humalog(I) (*Eli Lilly),*Inj100IU/ml(P.F Pen) Tk.4,397/3ml pen
Humalog mix 50/50(I)*(Eli Lilly),*Inj100IU/ml(P.F Pen)Tk.4,397/3ml pen
Insul Lispro *(Popular)*, Inj., cartidge100IU /ml Tk. 500.00/3 ml Cartridge

5.2.1.2 INTERMEDIATE AND LONG-ACTING INSULIN

When injected subcutaneously, an intermediate and long-acting insulin have an onset of action of approximately 1-2 hours, a maximal effect at 4–12 hours, and its duration of action is16–35 hours. Some are used twice daily in conjunction with soluble form and other only once *(see insulin regimens above)*. Various types are available. **Isophane Insulin** is a suspension of insulin with protamine. They are suitable for twice daily regime either as split mixed (mixing with soluble insulin) or pre/ready-mixed preparations. **Insulin Zinc Suspension (amorphous)** has an inter-mediate duration of action, and **Insulin Zinc suspension (Crystalline)** has a more prolonged duration of action. These preparations may be used independently or as pre-mixed Insulin Zinc suspension (30% amorphous, 70% crystalline). **Protamine Zinc Insulin** is usually given once daily in conjunction with soluble insulin. It has the drawback of binding with soluble insulin when mixed in the same syringe.

BIPHASIC INSULINS[ED]

(Other name: Biphasic Isophane Insulin)

A sterile buffered suspension of porcine insulin complexed with protamine sulphate in a solution of porcine insulin or a sterile buffered suspension of human insulin complexed with protamine sul-phate in a solution of human insulin.

Indications: diabetes mellitus

Cautions; Side effects: *see under soluble insulin*; protamine may cause allergic reactions. *Should be dispensed under prescription only*

Dose: *by subcutaneous injection,* according to the patient's response

Proprietary Preparations
Humulin 70/30(I) *(Eli Lilly)*, Inj. 100 IU/ml.Tk.310.00/10ml vial;Tk.336.00/3ml cartidge
Insulin Mixtard 30 *(Novo Nordisk),* Inj. 100 IU/ml, Tk.422.15/10ml vial; 40IU/ml. Tk.198.36/10ml vial
Insulin Mixtard 30(I) *(Novo Nordisk),* Inj. (penfill)100 IU/ml.Tk.374.58/3ml cartidge;
Insulin Mixtard 50(I) *(Novo Nordisk),* Inj., (penfill)100 IU/ml.Tk.374.58/3ml cartidge
Ansulin 30/70 *(Square),* Inj., Cartridge 100 IU/ml Tk. 225.83/3ml cartidge; vial Tk. 422.15/10 ml ;40IU/ml ,Tk. 198.36/10 ml
Ansulin 50/50 *(Square),* Inj., Cartridge 100 IU/ml Tk. 225.83/3ml cartidge; vial 100IU/ml,Tk. 422.15/10 ml ;40IU/ml ,Tk. 198.36/10 ml
Diasulin 30/70 *(ACI),* Inj.,vial 100 IU/ml Tk. 422.15/10 ml ;Inj., 40 IU Tk. 198.36/10 ml
Diasulin 50/50 *(ACI),* Inj., 100 IU/ml Tk. 422.15/10 ml ; Inj.,40 IU /mlTk. 198.36/10 ml
Insulet 30/70 *(Aristo),* Inj.,vial 100 IU/ml.Tk. 169.70/4 ml ; TK.415.00/10 ml
Insulet 50/50 *(Aristo),* Inj.,vial 100 IU/ml.Tk. 169.70/4 ml ;Tk. 415.00/10 ml

Insul 30/70 *(Popular)*, Inj.,vial100IU/ml Tk. 415.00/10 ml; Tk. 210.00/5 ml;40IU Tk. 195.00/10 ml; 112.27/5 ml
Insul 50/50 *(Popular)*, Inj., 100IU/ml Tk. 415.00/10 ml ;Inj., 40IU/mlTk. 195.00/10 ml
Maxsulin 30/70 *(Incepta)* Inj.,100IU/ml Tk. 357.73/10 ml; pen Tk222.00/pen ; vial40IU/mlTk. 168.09/10ml
Maxsulin 50/50(Incepta) Inj.,vial100IU/ml Tk. 415.00/10ml;pen,Tk.222.00/pen
Insuman-Comb *(Sanofi),* Inj., Tk. 281.70/5 ml; Tk. 287.00/3 ml Cartridge

ISOPHANE INSULIN[ED]

(Other names: Isophane Insulin; Isophane Protamine Insulin; Isophane Insulin-NPH).

A sterile suspension of bovine or porcine insulin or of human insulin in the form of a complex obtained by the addition of protamine sulphate.

Indications: diabetes mellitus (for intermediate action)

Cautions; Side effects: *see under soluble insulin*; protamine may cause allergic reactions

Interactions: *see Appendix-2*

Dose: *by subcutaneous injection,* according to the patient's response

Proprietary Preparations

Humulin N (I) *(Eli Lilly),* Inj.,100IU, Tk.680/10ml vial;Tk.310.00/4ml vial;Tk. Tк.336.00/3 ml cartridge
Insulin Insularated *(NovoNordisk),* Inj. 40IU/ml, Tk. 198.36/10ml vial; 100 IU/ml, Tk. 422.15/10ml vial
Insuman basal (I) *(Aventis),* Inj. 100 IU/ml, Tk. 259.69/10 ml
Insulatard Penfill(I) *(NovoNordisk*) Inj. 374.58/3ml cartridge
Insul N*(Popular)*, Inj.,vial 100IU Tk. 415.00/10 ml ;40 IUTk. 195.00/5 ml ; Cartridge 100IU/ml Tk. 222.00/3 ml
Ansulin N *(Square),* Inj., Cartridge 100 IU/ml Tk. 223.79/3 ml Cartridge; vial,100 IU/ml Tk. 422.15/10 ml;40IU Tk. 198.36/10 ml
Diasulin N *(ACI),* Inj.,vial 100IU Tk. 422.15/10 ml ;40IUTk. 198.36/10 ml
Insulet N *(Aristo),* Inj., vial, 40IU, Tk.172.00/4ml; Tk.195/10ml 100IUTk. 422.00/10 ml; .Tk. 172.00/4 ml
Maxsulin *(Incepta)* Inj.,vial 100IU Tk. 415.00/10 ml ;40IUTk. 195.00/10 ml

INSULIN ZINC SUSPENSION

(Other names: Insulin Zinc suspension [Mixed]; I.Z.S.)

A sterile neutral suspension of bovine and/or porcine insulin or of human insulin in the form of a complex obtained by the addition of a zinc salt; may be amorphous or microcrystalline consisting of rhombohedral crystals.

Indications: diabetes mellitus (long-acting)

Cautions; Side effects: *see under soluble insulin*

Interactions: *see Appendix-2*

Dose: *by subcutaneous injection*, according to the patient's response

Generic Preparation

Injection,100IU

INSULIN GLARGINE, DETEMIR

Indications: diabetes mellitus
Cautions; Side effects: *see under soluble insulin*

Dose: *by subcutaneous injection,* ADULT and CHILD over 6years, according to requirements

Note. sustained 24 hour duration of action allows dosing independently of meals

Proprietary Preparations

Lantus(I)*(Aventis),*inj.100IU/ml, Tk.1,025.74/3ml cartridge
Lantus Cartridge(I) *(Sanofi),* Inj., Cartidge,100IU Tk. 711.20/3 ml
Lantus SoloStar (I)*((Sanofi),* Inj.,100IU Tk. 1117.54/3 ml
Lantus Optiset(I) *(Sanofi),* Inj.,100IU Tk. 5395.75
Levemir FlexPen(I)*((Novo Nordisk),*Inj.,, (P.F.Pen) 100U/ml Tk.1305/pen
Insul Glargine *(Popular)*, Inj.,Cartidge,100IU Tk. 600/3 ml
Insulet GN *(Aristo),* Inj.100IU,Tk.600/3 ml vial
Glarine *(ACI),* Inj., 100IU Tk. 610.34/3 ml vial
Vibrenta *(Incepta),* Inj., 100IUTk. 600/10 ml
Vibrenta Penset *(Incepta),* Inj., 100IU Tk.600/Penset

INSULIN DEGLUDEC

Indications: diabetes mellitus
Cautions; Side effects: *see under soluble insulin*

Dose: *by subcutaneous injection,* ADULT and CHILD over 6years, according to requirements

Note. sustained 40 hour duration of action allows dosing independently of meals

Proprietary Preparation
Tresiba flex touch (I) *(Novo-nordisk), I*nj. 100IU/ml, Tk.2490.00/3ml pen

PROTAMINE ZINC INSULIN
(Other name: Insulin P.Z)

A sterile suspension of insulin in the form of a complex obtained by the addition of protamine and zinc chloride.

Indications: diabetes mellitus (long-acting)

Cautions; Side effects: *see under soluble insulin and notes above*; protamine may cause allergic reactions. **Interactions:** *see Appendix-2*

Dose: *by subcutaneous injection,* according to the patient's response

Generic Preparation
Injection., 100IU

5.2.2 ORAL ANTIDIABETIC AGENTS

5.2.2.1 SULPHONYLUREAS
5.2.2.2 BIGUANIDES
5.2.2.3 OTHER ORAL ANTI-DIABETIC DRUGS

A number of oral hypoglycaemic agents are used in the treatment of type 2 DM. These should be used to augment the effect of diet modification. They should not be prescribed until within three months it is seen that the patient does not respond adequately to diet control. Sulfonylureas and biguanides are the common oral antidiabetic drugs, though there are also other agents. They should be avoided in patients with renal impairment and also in condition likely to predispose lactic acidosis, severe dehydration, infection, hepatic impairment, pregnancy and breast-feeding.

5.2.2.1 SULFONYLUREAS

The sulfonylureas act mainly by augmenting insulin secretion. They are effective only when some residual beta cell activity is present. During long-term administration they also have some extra-pancreatic effect. All may cause hypoglycemia though uncommon except with high dose; hypoglycemia may persist for several hours. There are several sulphonylureas, all being similar in effectiveness. **Chlorpropamide** has a very long duration of action but has more side effects including unpleasant flashes after alcohol consumption. Selection of an individual sulphonylurea depends on the age of the patient, renal function, or more generally on personal experience. Elderly patients are prone to develop severe hypoglycemia when taking long-acting drugs such as **chlorpropamide** and **glibenclamide.** They should be replaced by short acting oral hypoglycemic agents such as **Gliclazide** or **tolbutamide.**

Cautions; Contraindications: These drugs tend to encourage weight gain and should be prescribed after trial with appropriate diet control and exercise. They should not be used during breast-feeding. Caution is needed in elderly and those with hepatic and renal impairment because of hazards of hypoglycemia. The short-acting tolbutamide may be used in renal impairment, as may be gliclazide and gliquidone, which are metabolised and inactivated in the liver. Sulphonylureas should be avoided in porphyria. Insulin therapy should be introduced temporarily during inter-current illness (such as myocardial infarction, coma, infection, and trauma) and during surgery since control of diabetes with sulphonylureas is often

inadequate in such circumstances. Insulin therapy is also substituted during pregnancy. Sulphonylurea therapy is contraindicated in presence of ketoacidosis.

Side effects: These are generally mild and infrequent and include gastrointestinal disturbances and headache. Chlorpropamide may cause facial flashing after drinking alcohol. It may also enhance sensitivity of antidiuretic hormone and rarely cause hyponatraemia. Sensitivity reactions (usually in first 6-8 weeks of therapy) include transient rashes which rarely progress to erythema multiforme and exfoliative dematitis, fever, and jaundice; photosensitivity has also been reported with chlorpropamide. Blood disorders are rare but include thrombocytopenia, agranulocytosis, and aplastic anemia.

GLIBENCLAMIDE[ED]

Indications: diabetes mellitus (Type 2 DM)

Cautions; Contraindications; Side-effects: *see notes above*

Interactions: *see Appendix-2*

Dose: Initially 5 mg daily (for elderly patients 2.5 mg, *see note above*), adjust according to response; maximum 15 mg daily; taken with breakfast

Proprietary Preparations

Dibenol *(Square),* Tab., 5 mg, Tk. 0.34/Tab.
Dicon *(Jayson),* Tab., 5 mg, Tk. 0.28/Tab.
Glaiden *(Amico),* Tab., 5 mg, Tk. 0.28/Tab.
Glibeno *(Albion),* Tab., 5 mg, Tk. 0.30/Tab.
Glucon *(Opsonin),* Tab., 5 mg, Tk. 0.26/Tab.
Gluconil *(Acme),* Tab., 5 mg, Tk. 0.28/Tab.

GLICLAZIDE[ED]

Indications: diabetes mellitus (Type 2 DM)

Cautions; Contraindications; Side-effects: *see notes above*

Interactions: *see Appendix-2*

Dose: initially 40-80 mg daily, adjust according to response; up to 160 mg as a single dose, taken before breakfast; higher dose to be divided; maximum 320 mg daily

Proprietary Preparations

Admira *(Unimed),* MR Tab., 30 mg, Tjk. 6.00/Tab.;Tab. , 80 mg, Tk. 6.00/Tab.
Comprid *(Square),* Tab., 80 mg, Tk. 7.00/Tab; 30 mg, Tk. 6.02/Tab.; 60 mg, Tk. 11.00/Tab.
Consucon *(Incepta),* MR Tab., 30 mg, Tk. 6.00/Tab. ;Tab. , 80 mg, Tk. 7.00/Tab.
Diab *(Rephco),* Tab., 80 mg, Tk. 6.00/Tab.
Diaprid *(Alco),* Tab., 80 mg, Tk. 6.00/Tab.
Diapro *(Beximco),* Tab., 80 mg, Tk. 7.00/Tab.; MR Tab. , 30 mg, Tk. 7.00/Tab.
Diatrol *(Pacific),* MR Tab., 30 mg, Tk. 6.02/Tab. ; Tab., 80 mg, Tk. 6.02/Tab.; Tab., 80 mg, Tk. 6.02/Tab.
Diazid *(Nipro JMI),*Tab., 80 mg, Tk. 6.00/Tab.
Dimerol *(Drug Int),* Tab., 80 mg, Tk. 7.00/Tab.; MR Tab., 30mg, Tk. 6.00/Tab.
G-gliclazide *(Gonoshasthaya),* Tab. 80 mg, Tk. 4.00/Tab.
Gl *(Central),* Tab., 80 mg, Tk. 7.00/Tab.
Glad *(Novartis),* Tab., 80 mg, Tk. 7.00/Tab.
Gle *(Asiatic),* Tab., 80 mg, Tk. 11.00/Tab.
Gliclid *(Acme),* MR Tab., 30 mg, Tk. 7.00/Tab.;Tab., 80 mg, Tk. 3.6/Tab.
Glicron *(Renata),* Tab., 80 mg, Tk. 7.00/Tab.; CR Cap., 30mg, Tk. 6.02/Cap.
Glimicron *(White Horse),* Tab. 80 mg, Tk. 7.00/Tab.;MR Tab., 30 mg, Tk. 6.00/Tab.
Glirol *(Albion),* Tab., 80 mg, Tk. 6.00/Tab.
Glitab *(Hudson),* Tab., 80 mg, Tk.4.50/Tab.
Glitz *(Sharif),* Tab., 80 mg, Tk. 7.00/Tab.
Glix *(Navana),* Tab., 80 mg, Tk. 8.00/Tab.
Glizid *(Opsonin),*Tab., 80 mg, Tk. 5.26/Tab.;MR Tab., 30 mg, Tk. 4.53/Tab.
Glucoact *(Veritas),* Tab., 80 mg, Tk. 6.00/Tab.
Glucocare *(Doctor TIMS),* Tab., 80 mg, Tk. 7.00/Tab.
Glucostat *(Biopharma),* Tab. , 80 mg, Tk. 7.00/Tab.
Glucozid *(Aristo),* Tab. , 80mg, Tk. 7.00/Tab.
Gluzit *(Popular),* Inj., 80 mg, Tk. 7.00/Tab.
Gored *(General),* MR Tab., 30 mg, Tk. 8.83/Tab.;Tab. , 80 mg, Tk. 7.00/Tab.
Kezid *(Kemiko),* Tab., 80 mg, Tk. 8.00/Tab. ;MR Tab. , 30 mg, Tk. 8.00/Tab.
Likazid *(Amico),* Tab., 80 mg, Tk. 4.90/Tab.
Lozide *(ACI),* Tab., 80 mg , Tk. 7.00/Tab.
Oclazid*(Orion),* MR Tab., 30 mg, Tk. 6.02/Tab.; Tab. , 80 mg, Tk. 7.00/Tab.
Onzid *(Leon),* Tab., 30 mg, Tk. 6.00/Tab. ; Tab. , 80 mg, Tk. 8.00/Tab.
Orazid *(Somatec),* Tab., 80 mg, Tk. 7.00/Tab.
Sinazid *(Ibn Sina),* Tab., 80 mg, Tk. 6.50/Tab.
Sucleer *(RAK),* Tab., 80 mg, Tk. 8.0/Tab.;MR Tab., 30 mg, Tk. 8.00/Tab.
Sucotab *(Globe),* Tab., 80 mg, Tk. 7.00/Tab.
Sugred *(Ad-din),* Tab., 80 mg, Tk. 6.00/Tab.
Xido *(Delta),* Tab., 80 mg, Tk. 7.00/Tab.

GLIMEPIRIDE

Indication: type 2 DM
Cautions: *see notes above*
Contra-indications: *see notes above*
Interactions: *see Appendix-2*
Side-effects: *see notes above*
Dose: initially 1 mg daily; adjusted according to response in 1mg steps at 1-2 week intervals; usual max 4mg daily (exceptionally up to 6mg daily may be used);taken shortly before or with first meal

Proprietary Preparations
Adglim *(Unimed),* Tab., 1 mg, Tk.3/Tab.; 2mg, Tk. 5/Tab.
Amaryl *(Sanofi),* Tab., 1 mg , Tk. 6.90/Tab.; 2mg, Tk. 12.90/Tab.; Tab., 3 mg, Tk. 16.50/Tab.; Tab., 4 mg, Tk. 21/Tab.
Condia *(RAK),* Tab., 1 mg, Tk.4.50/Tab.; Tab., 2 mg, Tk. 8/Tab.;Tab., 3mg, Tk. 10/Tab.
Dactus *(Acme),* Tab., 1 mg, Tk. 3/Tab.; Tab., 2 mg, Tk. 5.01/Tab.; 3 mg, Tk. 7.02/Tab.
Dialon *(Eskayef),* Tab, 1 mg, Tk. 3/Tab.; 2mg, Tk. 5/Tab.; 4 mg , Tk. 8/Tab.
Diaryl *(Beximco),* Tab. , 1 mg, Tk. 4.50/Tab.; 2 mg, Tk. 8.00/Tab.; 3 mg, Tk. 10.00/Tab.
Dieta *(Pacific),* Tab., 1 mg, Tk. 3.76/Tab.; 2 mg, Tk. 6.02/Tab.; 3 mg, Tk. 7.52/Tab. ; 4 mg, Tk. 9.02/Tab.
Gipid *(Alco),* Tab., 1 mg, Tk. 3.00/Tab. ; 2 mg, Tk. 5.00/Tab.
Glaryl *(Ad-din),* Tab., 1 mg, Tk. 2.50/Tab.; 2 mg, Tk. 4.00/Tab.
Glimepiride *(Albion),* Tab., 1 mg, Tk. 3.00/Tab.; 2 mg, Tk. 5.01/Tab.
Glimirid *(ACI),* Tab.,1 mg , Tk. 4.50/Tab.; 2 mg , Tk. 8.00/Tab.; 3 mg , Tk. 10.00/Tab.; Tab. , 4 mg , Tk. 12.00/Tab.
Glims *(Opsonin),*Tab.,1 mg, Tk. 3.38/Tab.;Tab.,2 mg,Tk. 5.26/Tab.
Glirid *(General),*Tab., 1 mg, Tk. 3.01/Tab.; 2 mg, Tk. 5.02/Tab.
Gluconor *(Aristo),*Tab.,1 mg, Tk. 4.50/Tab.; Tab., 2 mg, Tk. 8.00/Tab.
Glucorid *(Biopharma),*Tab.,1 mg, Tk. 3.00/Tab.; Tab., 2 mg, Tk. 5.00/Tab.
Limaryl *(Popular),*Tab.,3 mg, Tk.7.03/Tab.; 4 mg, Tk. 8.03/Tab.
Limpet *(Drug Int.),* Tab., 2 mg, Tk. 5.00/Tab.; 3 mg, Tk.7.00/Tab.; 4 mg, Tk. 9.00/Tab. ; 1 mg, Tk. 3.00/Tab.
Losucon *(Incepta),* Tab.,1 mg, Tk. 4.50/Tab.; 2 mg, Tk. 8.00/Tab.; 3 mg, Tk. 10.00/Tab. ; 4 mg , Tk. 12.00/Tab.
Pride *(White Horse),* Tab.,1 mg, Tk.3.30/Tab.; 2 mg, Tk.5.00/Tab.
Secrin *(Square),* Tab., 1 mg, Tk. 4.50/Tab.; 2 mg, Tk. 8.00/Tab.; 3 mg ,Tk. 10.00/Tab.; 4 mg, Tk. 12.00/Tab.
Stimulin *(Orion),* Tab.,1 mg, Tk. 3.01/Tab.; 2 mg, Tk. 5.02/Tab.

GLIPIZIDE

Indications: type 2 DM

Cautions; Contraindications; Side-effects : *see notes above*

Interactions: *see Appendix-2*

Dose: initially 2.5-5.0 mg daily, adjust according to response; up to 15 mg as a single dose, taken before breakfast; higher dose to be divided; maximum 40 mg daily

Proprietary Preparations
Diactin *(Beximco),* Tab., 5 mg, Tk. 1.50/Tab.
Diaplus *(Pacific),* XR Tab., 5 mg, Tk. 2.11/Tab.; Tab., 5 mg, Tk. 1.50/Tab.
Diazipi *(Medimet),* Tab. 2.5 mg, tk. 1.00/Tab.; 5 mg, Tk. 2.00/Tab.
Gipix *(Doctor TIMS),*Tab., 5 mg, Tk. 2.00/Tab.
Glimerol *(Drug Intl),* Tab., 5 mg, Tk. 1.50/Tab.
Glipizied *(Albion),* Tab., 5 mg, Tk. 2.00/Tab.

5.2.2.2 BIGUANIDES

Metformin is the only available biguanide for the treatment of diabetes mellitus. It acts by reducing the basal hepatic glucose output mainly by suppression gluconeogenesis. It also reduces gastro-intestinal absorption of glucose and increases glucose utilization in the cells by potentiating insulin action. Metformin is the drug of choice in obese patients, inadequately controlled with diet and/or sulphonylurea. The advantages include absence of hypoglycaemia and decrease in weight gain. Metformin may provoke lactic acidosis, which is most likely to occur in patients with kidney diseases, but the condition is very rare. If it occurs, 50 percent of the cases become fatal. Hypoglycaemia is not a problem with metformin; it is therefore called an oral anti-hyperglycaemic agent rather than an oral hypoglycaemic agent. The advantages include lower incidence of hypoglycemia and weight gain.

Gastrointestinal side effects are usually common and may persist in some patients. Metformin may provoke lactic acidosis, which is most likely to occur in patients with kidney diseases.

Extended release formulation of metformin has now been developed to provide better glycaemic control over 24 hours. It is well-tolerated and gastrointestinal side-effects like nausea and diarrhoea are less marked than conventional metformin.

METFORMIN HYDROCHLORIDE [ED]

Indications: diabetes mellitus, especially in obese patients with TYPE 2 DM. It may be used alone or in combination with sulphonylurea or with insulin where resistance is dominant (as in acromegaly or Cushing's syndrome)

Cautions: is not recommended during pregnancy and should be used only if clearly needed while breast-feeding; it should not be used in patients with pre-existing liver disease, kidney disease or any allergies

Contraindications: *see notes above*

Interactions: *see Appendix-2*

Side-effects: gastrointestinal upset like loss of appetite, nausea, abdominal discomfort and diarrhoea, lactic acidosis, metallic taste, vitamin B_{12} and Folic acid deficiency with prolonged use

Dose: 500 or 850 mg daily 8 hourly; taken during meals; maximum 3 g daily

Proprietary Preparations

Bigmet *(Renata),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.
Comet *(Square),* Tab. , 500 mg, Tk. 3.00/Tab.; 750 mg, Tk. 3.50/Tab.; 850 mg, Tk. 4.50/Tab.; 1 gm, Tk. 5.00/Tab.; XR Tab., 500 mg, Tk. 5.00/Tab.; 1 gm, Tk. 7.02/Tab.
Daomin *(Acme),* Tab., 500 mg, Tk. 2.99/Tab.; 850 mg, Tk. 4.98/Tab.; 1 gm, Tk. 5.85/Tab.; XR Tab., 500 mg, Tk. 5.00/Tab.; 1 gm, Tk. 7.00/Tab.
Dia-M *(Medimet),* Tab., 850mg, Tk.2.50/Tab.; 500 mg, Tk.1.10/Tab.
Diout *(Asiatic),* Tab. , 850 mg, Tk. 2.25/Tab.
Etform *(Novartis),* Tab., 500 mg, Tk. 3.20/Tab.; 850 mg, Tk.5.50/Tab.
Formet *(Biopharma),* Tab., 500 mg, Tk. 4.00/Tab.; 850 mg, Tk. 6.00/Tab.
Glucomet *(Aristo),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 6.00/Tab.; XR Tab., 500 mg, Tk. 6.00/Tab.; 750 mg, Tk. 8.00/Tab.
Glucomin *(Nipro JMI),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 5.00/Tab.
Glunor *(Eskayef),* Tab, 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.; XR Tab, 500 mg, Tk. 4.00/Tab.
Glymin *(Healthcare),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.; XR Tab., 500 mg, Tk. 5.00/Tab.
G-Metformin *(Gonoshasthaya),* Tab., 500 mg, Tk. 2.50/Tab.; 850 mg, Tk. 4.25/Tab.
Guamin *(Ad-din),* Tab., 850 mg, Tk. 3.00/Tab.
Hi-Met *(Hudson),* Tab., 850 mg, Tk.3.00/Tab.
Informet *(Beximco),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.50/Tab.; LA Tab., 500 mg, Tk. 5.00/Tab.; 750 mg, Tk. 7.00/Tab.
Insimet *(Ibn Sina),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.; XR Tab., 500 mg, Tk.5.00/Tab.
Kemin *(Kemiko),* Tab., 500mg, Tk. 2.50/Tab.850 mg, Tk. 4.00/Tab.; SR Tab., 500 mg, Tk. 5.00/Tab.
Meforex *(Jayson),* Tab., 500 mg, Tk. 2.00/Tab.; 850 mg, Tk. 3.00/Tab.
Meforin *(RAK),* Tab., 500 mg, Tk. 4.00/Tab.; 850 mg, Tk. 6.00/Tab.; XRTab., 500 mg, Tk. 7.00/Tab.
Meformin *(Organic),* Tab., 500 mg, Tk. 2.00/Tab.; 850 mg , Tk. 3.00/Tab.
Meglu *(Unimed),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.; ER Tab., 500 mg, Tk. 5.00/Tab.
Met *(Opsonin),* Tab., 500 mg, Tk. 2.26/Tab.; 850 mg, Tk. 3.76/Tab.; XR Tab., 500 mg, Tk. 3.02/Tab.; 750 mg, Tk. 4.53/Tab.; 1 gm, Tk. 5.29/Tab.
Metarin *(Popular),* Tab., 500 mg, Tk. 2.51/Tab.; 850 mg, Tk. 4.02/Tab.
Metfar *(White Horse),* Tab., 500mg, Tk. 4.00/Tab.; 850 mg, Tk. 5.00/Tab.; SR Tab., 500 mg, Tk. 4.00/Tab.
Metfo *(Pacific),* Tab., 500 mg, Tk. 3.01/Tab.; 850 mg, Tk. 4.51/Tab.; XR Tab., 500 mg, Tk. 5.26/Tab.
Metform *(ACI),* Tab., 500 mg , Tk. 3.00/Tab.; 850 mg , Tk. 4.50/Tab.; ER Tab., 500 mg , Tk. 5.00/Tab.; 1 gm, Tk.7.03/Tab
Metmin *(Alco),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.
Metomin *(Somatec),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 5.00/Tab.
Metsa *(Sanofi),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 5.00/Tab.; XR Tab., 500 mg, Tk. 6.00/Tab.
M-Form *(Central),* Tab., 850 mg, Tk. 5.50/Tab.

M-Fort *(Albion),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.; XR Tab., 500 mg, Tk. 5.00/Tab.
M-Min *(Sharif),* Tab., 500 mg, Tk. 3.00/Tab.
Nobesit *(Incepta),* Tab., 500 mg, Tk.3.00/Tab.; 850 mg, Tk.4.50/Tab.; 1 gm, Tk.7.00/Tab.; XR Tab., 500 mg, Tk.5.00/Tab.
Nvmet *(Navana),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 5.00/Tab.; SR Tab., 500 mg, Tk. 5.00/Tab.
Obid *(Delta),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 5.00/Tab.
Onmet *(Leon),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 5.00/Tab.
Oramet *(Drug Intl),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.; SR Tab., 500 mg, Tk. 5.00/Tab.; 1 gm, Tk. 7.00/Tab.
Ormin *(Orion),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 5.00/Tab.
Ruzmet *(Amico),* Tab., 500 mg, Tk. 3.00/Tab.
Sucomet *(Globe),* Tab., 500 mg, Tk. 3.00/Tab.:850 mg, Tk. 4.50/Tab.
Sugamet *(General),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, 4.50/Tab.
Verimet *(Veritas),* Tab., 500 mg, Tk. 3.00/Tab.; 850 mg, Tk. 4.00/Tab.

Metformin Hydrochloride + Glipizide
Metglip *(Pacific),* Tab., 250 mg + 2.5 mg, Tk. 1.88/Tab.; 500 mg + 2.5 mg, Tk. 3.01/Tab.; 500 mg + 5 mg, Tk. 3.76/Tab.
Metazid *(Popular),* Tab., 500 mg + 2.5 mg, Tk. 2.51/Tab.
Mefoglip *(Incepta),* Tab., 250 mg + 2.5 mg, Tk. 1.90/Tab.; 500 mg + 2.5 mg, Tk. 2.80/Tab.; 500 mg + 5 mg, Tk. 3.70/Tab.

5.2.2.3 OTHER ORAL ANTIDIABETIC AGENTS

Incretin mimetics (GLP 1 agonist and DPT-4 inhibitors) lowers blood glucose by a) reducing hepatic glucose production by increasing insulin secretion plus reducing glucagons secretion; b) slowing gastric emptying and c) reducing appetite. It can be used as monotherapy or in combination with secret/gauges/insulin. **GLP 1 agonists** (Exenatide & Liraglutide**)** are very effective in obese person because of their predominant reducing appetite action and **DPT-4 inhibitors** (Sitagliptins, vildagliptin, linagliptin, Saxagliptin) are effective by DPT-4 enzyme activity.

Acarbose an inhibitor of alpha glucosidase delays the digestion and absorption of starch and sucrose. It has small but significant effect in lowering blood glucose and is used as an adjunct to metformin and sulfonylureas. Postprandial hyperglycemia in Type-1DM can be reduced by acarbose. Flatulence is a troublesome side-effect of acarbose at times.

Among other new agents, **Repaglinide** stimulates insulin release, has a rapid onset and short duration of action. It may be used in Type 2 DM which is inadequately controlled by diet and exercise; it may also be given with metformin.

Among thiazolidindione oral hypoglycaemic agents are included **pioglitazone** and **rosiglitazone.** They reduce peripheral insulin resistance leading to a reduction of blood glucose level. These drugs are recommended for use in combination with metformin and sulfonylureas. Inadequate response to a combination and sulphonylurea may indicate failing insulin release; pioglitazone or rosiglitazone has a limiting role in these circumstances and insulin treatment should not be delayed. Long term benefit of thiozolidindiones has not yet been confirmed.

ACARBOSE

Indications: diabetes mellitus inadequately controlled by diet with or without other antidiabetic agent

Cautions: monitor liver function **Contraindications and Side-effects:** pregnancy and breast-feeding, inflammatory bowel disease (ulcerative colitis, Crohn's disease), hepatic impairment, severe renal impairment

Interactions: *see Appendix-2*

Dose: initially 50 mg daily, increased up to 100 mg three times daily slowly; single dose taken with breakfast, higher doses divided; maximum 600 mg daily. CHILD under 12 years not recommended

Proprietary Preparations
Carbos *(Ibn Sina),* Tab. 50mg.Tk 8/Tab

Gluco*(Acme),* Tab.100mg, Tk. 20/Tab; 50mg.Tk.11/Tab
Sugatrol *(Pacific),* Tab. 50mg Tk.8/Tab

MIGLITOL

Indications: treating type 2 diabetes alone or in combination with a sulfonylurea such as glyburide
Side Effects: diarrhea, bloating, soft stools, stomach pain
Cautions: pregnancy breast-feeding ,if the patient has stomach or bowel problems, liver disease, or kidney disease
Interactions:*see Appendix -2*
Dose: 25 mg three times daily and then increase after four to eight weeks to 50-100mg three times daily.

Proprietary Preparations
Diaset *(ACI)*,Tab 25mg, Tk10.04/Tab; 50 mg, 15.06/Tab.

NATEGLINIDE

Indications: lowering blood sugar levels in patients with type 2 diabetes. It used along with diet and exercise.
Cautions: type 1 diabetes, diabetic ketoacidosis, pregnancy & breast feeding; elderly
Side Effects: Dizziness; flu-like symptoms (fever, chills, sore throat); joint pain; upper respiratory tract infection. : changes in vision; headache; increased hunger; loss of consciousness; nervousness; seizures; shakiness; sweating; tiredness.
Dose:120 mg orally three times daily before meals

Proprietary Preparations
Starlex *(Novertis)*, Tab., 120mg, Tk.28.68/Tab.

PIOGLITAZONE

Indications: *see notes above*
Cautions: liver function tests to be carried out. There is risk of heart failure; so the drug should be used with caution in cardio-vascular disease
Side Effects: gastro-intestinal disturbances, weight gain, edema, anemia, headache, visual disturbance, dizziness, arthralgia, haematuria, impotence, less commonly hypoglycaemia, fatigue, sweating, altered blood lipids, proteinuria
Interactions: *see Appendix 2*
Dose: 15-30 mg once daily

Proprietary Preparations
Adpas *(General),* Tab., 15 mg, Tk. 8.03/Tab.
Diaglit *(Beximco),* Tab., 15 mg, Tk. 8.00/Tab.; 30 mg, Tk. 15.00/Tab.
Diapiotab *(Medimet),* Tab., 15mg, Tk.8.00/Tab.; Tab., 30mg, Tk.12.00/Tab.
Diatag *(ACI),* Tab., 15 mg, Tk. 8.03/Tab.; 30 mg, Tk. 15.00/Tab.; 45 mg, Tk. 18.00/Tab.
Glitazon *(Ibn Sina),* Tab., 15 mg, Tk. 8.00/Tab.
Glucozon *(Aristo),* Tab., 15 mg, Tk. 8.00/Tab.; 30 mg, Tk. 15.00/Tab.
Lit *(White Horse),* Tab., 15 mg, Tk. 8.00/Tab.; 30 mg, Tk. 9.00/Tab.
PGT *(Central),* Tab., 15 mg, Tk. 8.00/Tab.
Piglit *(Pacific),* Tab., 15 mg, Tk. 6.02/Tab.; 30 mg, Tk. 9.02/Tab.
Pigzon *(Sharif),* Tab., 15 mg, Tk. 8.00/Tab.; 30 mg, Tk. 15.00/Tab.
Piodar *(Incepta),* Tab., 15 mg, Tk. 8.00/Tab.; 30 mg, Tk. 15.00/Tab.
Piol *(Opsonin),* Tab., 15 mg, Tk. 6.04/Tab.; 30 mg, Tk. 11.32/Tab.
Saglit *(Sanofi),* Tab., 15 mg, Tk. 8.03/Tab.; 30 mg, Tk. 15.06/Tab.
Tos *(Square),* Tab., 15 mg, Tk. 8.04/Tab.; 30 mg, Tk. 15.00/Tab.

ROSIGLITAZONE

Indications: *see notes above*
Cautions: congestive heart failure, heart attack, chest pain, discomfort; hepatic impairment, pregnancy and breast feeding.
Side Effects: same as that of pioglitazone
Dose: 4mg once daily

Proprietary Preparations
Roglit *(Pacific),* Tab. 4 mg, Tk. 6.02/Tab.
Rosiglitazone + Metformin HCl
Rogmet *(Pacific),* Tab., 2 mg + 500 mg, Tk. 4.51/Tab.
Sensimet *(Square),* Tab., 1 mg + 500 mg, Tk. 4.01/Tab.; 2 mg + 500 mg, Tk. 6.02/Tab.
Metarin Plus *(Popular),* Tab., 1 mg + 500 mg, Tk. 4.02/Tab.

REPAGLINIDE

Indications: diabetes mellitus as monotherapy or in combination with metformin

Cautions: monitor liver function; not recommended for children/adolescent under 18 years and elderly over 70 years

Contra-indications and Side-effects: diabetic ketoacidosis; renal or hepatic impairment; pregnancy and breast-feeding

Interactions: *see Appendix-2*

Dose: initially 500 micrograms within 30 minutes before main meals, adjusted according to response at intervals of 1-2 weeks; maximum up to 15 mg daily

Proprietary Preparations

Glimet *(Drug Int),* Tab., 1 mg, Tk. 3.00/Tab.
Gluretor*(Pacific),* Tab., 0.5 mg, Tk. 2.11/Tab.; 1 mg, Tk 3.01/Tab.; 2 mg, Tk. 4.51/Tab.
Nomopil *(Incepta),* Tab. , 0.5 mg, Tk. 2.00/Tab.; 1 mg, Tk. 3.00/Tab., 2 mg, Tk. 5.00/Tab.
Prandil *(Unimed),* Tab.,1 mg,Tk. 3.00/Tab.
Premil *(Beximco),* Tab., 0.5 mg, Tk.2.00/Tab.;1 mg, Tk. 3.00/Tab.; 2 mg, Tk. 5.00/Tab.
Prifid *(White Horse),* Tab., 1 mg, Tk. 3.00/Tab.
Repaglid *(Alco),* Tab., 1 mg, Tk. 3/Tab.; 2mg, Tk.5/Tab.
Repanid *(Opsonin),* Tab., 1 mg, Tk. 2.26/Tab.; 2 mg , Tk.3.77/Tab.

INCRETIN MIMETICS

LINAGLIPTINE

Indications: type 2 diabetes in patients who cannot control blood sugar levels by diet and exercise alone. It is used along with diet and exercise. It may be used alone or with other antidiabetic medicines.

Cautions: type 1 diabetes & ketoacidosis; pregnancy & breast feeding

Side effects: headache, joint pain, runny or stuffy nose, sore throat; severe stomach or back pain.

Dose: 5 mg orally once a day

Proprietary Preparations

Adlina *(Unimed),* Tab., 5 mg, Tk. 30.00/Tab.
Lijenta *(Nipro JMI),* Tab., 5 mg, Tk. 30.00/Tab.
Linaglip *(Aristo),* Tab., 5 mg, Tk. 20.00/Tab.
Linarol *(Drug Intl),* Tab., 5 mg, Tk. 15.00/Tab.
Linatab *(Incepta),* Tab., 5 mg, Tk. 15.00/Tab.
Linita *(Square),* Tab., 5 mg, Tk. 15.00/Tab.

OTHER INCRETIN MIMETICS

Indications: diabetes mellitus inadequately controlled by diet with or without other antidiabetic agent

Cautions: drug allergy
Contraindications and Side-effects: impaired renal function (except linagliptin): GI upset, upper Respiratory Tract Infection and pancreatitis

Interactions: *see Appendix-2*

Dose: Sitagliptins (100 mg/day once; 50mg/day for CCR <50 ml/min, & 25 mg/day for CCR <30 ml/min)**, vildagliptin,** (50 mg once or twice/; 50mg/day for CCR <50 ml/min), **Saxagliptin** (2.5 mg/day once or twice ; 2.5mg/day for CCR <50 ml/min).

Proprietary Preparations:

Saxagliptin
Glyza *(Ibn Sina),* Tab. 2.5 mg, Tk. 20.00/Tab.; 5 mg, Tk. 35.00/Tab

Vidagliptin
Dialiptin *(Drug Int.),* Tab. ,50 mg, Tk. 15/Tab.
Galvus(I) *(Novartis),* Tab. 50 mg, Tk. 28/Tab.
Gluvan *(Aristo),* Tab., 50 mg, Tk. 20.00/Tab.
Vida *(Pacific),* Tab., 50 mg, Tk. 15.04/Tab.
Vigatin *(Eskayef),* Tab, 50 mg, Tk. 20.00/Tab.
Viglita *(Square),* Tab., 50 mg, Tk. 20.00/Tab.
Vildagil *(Sharif),* Tab., 50 mg, Tk. 18.00/Tab.
Vildapin*(Acme),* Tab., 50 mg, Tk. 15.00/Tab.
Vildus *(Opsonin),* Tab., 50 mg, Tk. 15.04/Tab.
Viptin *(General),* Tab., 50 mg, Tk. 20.00/Tab.

Vildagliptin + Metformin HCl
Dialiptin-M *(Drug Int.),* Tab., 50 mg + 500 mg, Tk. 16.00/Tab.; 50 mg + 850 mg, Tk. 17.00/Tab.
Galet-M *(White Horse),* Tab., 50 mg + 500 mg, Tk. 18.00/Tab.
Gluvan Plus *(Aristo),* Tab., 50 mg + 850 mg, Tk. 22.00/Tab. ;Tab. , 50 mg + 500 mg, Tk. 21.00/Tab.
Galvus Met *(Novartis),* Tab. 50 mg + 500 mg, Tk. 28/Tab.; 50 mg + 850 mg, Tk. 28Tab.

Vida Plus *(Pacific),* Tab., 50 mg + 500 mg, Tk. 16.54/Tab.; 50 mg + 850 mg, Tk. 18.05/Tab.
Viglimet *(Square),* Tab. , 50 mg + 850 mg, Tk. 23.00/Tab. ; 50 mg + 500 mg, Tk. 22/Tab.
Vildagil-M *(Sharif),* Tab. , 50 mg + 500 mg, Tk. 20/Tab.; 50 mg + 850 mg, Tk. 22/Tab.
Vildamet *(Opsonin),* Tab., 50 mg + 500 mg, Tk. 16.54/Tab.;Tab., 50 mg + 850 mg, Tk. 17.29/Tab.
Vildapin Plus *(Acme),* Tab., 50 mg + 500 mg, Tk. 16.00/Tab.;Tab., 50 mg + 850 mg, Tk. 17.00/Tab.
Viptin Plus *(General),* Tab. , 50 mg + 500 mg, Tk. 21.00/Tab.;Tab. , 50 mg + 850 mg, Tk. 22.00/Tab

Sitagliptin
Glipita *(Beximco),* Tab. , 100 mg, Tk. 47.00/Tab.; 50 mg, Tk. 24.00/Tab.
Incrit *(Sanofi),* Tab., 50 mg, Tk. 18.00/Tab.; 100 mg, Tk. 30.00/Tab.
Janvia *(Acme),* Tab., 100 mg, Tk. 28.00/Tab.; 50 mg, Tk. 15.00/Tab.
SGN *(Pacific),* Tab., 50 mg, Tk. 15.04/Tab.; Tab., 100 mg, Tk. 26.32/Tab.
Siglita *(Square),* Tab. , 50 mg, Tk. 18.00/Tab.; Tab. , 100 mg, Tk. 30.00/Tab.
Sigtil *(White Horse),* Tab. , 50 mg, Tk. 15/Tab
Sitagil *(Incepta),* Tab. , 100 mg, Tk. 28/Tab.; 25 mg, Tk. 8.00/Tab. ; 50 mg, Tk. 15/Tab.
Sitap*(ACI),* Tab. , 50 mg, Tk.15.00/Tab. ; 100 mg, Tk. 28.00/Tab.
Sliptin *(Drug Int.),* Tab., 100 mg, Tk. 28/Tab.; 25 mg, Tk. 8.00/Tab.; 50 mg, Tk. 15/Tab.

Sitagliptin+ Metformin
Glipita M *(Beximco),* Tab., 50 mg + 1 gm, Tk. 27/Tab.; Tab., 50 mg + 500 mg, Tk. 25/Tab.
Janmet *(Acme),* Tab.,50 mg + 1 gm, Tk. 18/Tab.;Tab., 50 mg + 500 mg, Tk. 16/Tab.
SGN Plus*(Pacific),* Tab., 50 mg + 500 mg, Tk. 18.80/Tab.
Siglimet *(Square),* XR Tab. , 50 mg + 500 mg , Tk. 21.00/Tab.; XR Tab. , 50 mg + 1 gm , Tk. 23.00/Tab.;Tab. , 50 mg + 500 mg , Tk. 20.00/Tab.; 50 mg + 1 gm, Tk. 22.00/Tab.
Sigtil-M *(White Horse),* Tab., 50 mg + 500 mg, Tk. 28.00/Tab.
Sitagil M *(Incepta),* ER Tab., 50 mg + 1 gm, Tk. 18.00/Tab.; ER Tab., 50 mg + 500 mg, Tk. 16.00/Tab.
Sitomet *(ACI),* Tab., 50 mg + 500 mg, Tk. 16.00/Tab.; 50 mg + 1 gm, Tk. 18.00/Tab.
Sliptin-M *(Drug Int.),* Tab., 50 mg + 1 gm , Tk. 18.00/Tab. ; 50 mg + 500 mg, Tk. 16.00/Tab.

5.2.3 DIABETIC EMERGENCY

5.2.3.1 DIABETIC KETOACIDOSIS (DKA)
5.2.3.1 HYPOGLYCAEMIA

5.2.3.1 DIABETIC KETOACIDOSIS (DKA)

Diabetic Ketoacidosis (DKA) is a medical emergency in diabetics often found in Typ1 DM and also in stressful situation in other types of diabetes. It results from lack of insulin leading to hyperglycaemia and ketoacidosis. Its causes are: omission or reduction of insulin dose; undiagnosed diabetes; and intercurrent illness, especially acute infection. **Soluble insulin** given intravenously, is used in the management of DKA. If infusion pump is available, infuse at a rate of 3-6 units per hour. Alternately, give intramuscularly 10-20 units, followed by hourly 5-10 units. Hourly fall of blood sugar should be in the range of 3-6 mmol/L. Usual subcutaneous regime of insulin may be started when blood glucose falls below 15 mmol/L.

Intravenous replacement of fluid and electrolytes is an essential part of the management of ketoacidosis. **Normal Saline** is infused initially at 1 litre per hour, and then the rate is calculated against clinical status. If blood level of K^+ is < 3 mmol/L, infuse at a rate of 39 mmol/hr; if blood level is 3-4 m mol/L, infuse at a rate of 26 mmol/hr; if blood level is 5-6 mmol/L, infuse at a rate of 13 mmol/hr; and if blood level is more than 6 mmol/L, stop infusion. **Sodium bicarbonate** infusion is only used in cases of extreme acidosis and shock. In patients with severe acidosis (bicarbonate less than 15 mmol/L), infuse 500 ml of 1.4% Sodium bicarbonate and consider extra potassium supplement. **Glucose** solution (5%) is infused if the blood glucose level falls below 10 mmol/L but insulin infusion must continue.

5.2.3.2 HYPOGLYCAEMIA

The most frequent complication of insulin therapy and of high doses of sulphonylureas is hypoglycemia and it occurs when blood sugar becomes very low (less than 50 mg/litre). Patients need to be educated about its warning symptoms and treatment. Warning signs include hunger pain, sweating, tremor, light headedness and dizziness. Later on patients develop behavioral and sensorial changes with subsequent coma and even convulsions if uncorrected. Unfortunately some patients especially those with neuropathy or on beta blocker therapy do not experience the early warning signs. Common causes of hypoglycaemia in a diabetic are: unusual excessive exercise; delay or omission of a snack or meal; administration of too much of insulin (especially in intramuscularly); excess intake of sulphonylurea; over indulgence in alcohol; and severe impairment of renal function. Mild and to moderate hypoglycaemia may be treated by the patient himself/herself or by a family member with sugar or a glass of soft drinks or fruit juice or biscuit, chocolate or honey. If the symptoms reappear within half an hour, repeat the treatment or let the patient take the next meal. In severe hypoglycaemia with unconsciousness (stupor, coma or seizures), **intravenous dextrose** (25%) should be given by infusion through a large-gauge needle. If recovery does not occur, search for additional causes. Frequent blood glucose monitoring will help to prevent severe hypoglycaemia.

Glucagon may be given (1 mg intramuscularly or intravenously) as an alternative to parenteral glucose. It increases plasma glucose concentration by mobilizing glycogen stored in the liver. If there is no response within 10 minutes, intravenous glucose must be given. In nocturnal hypoglycaemia, reduce the dose of insulin or change the timing of evening insulin dose with dinner time. These adjustments are made in conjunction with blood glucose monitoring.

GLUCAGON

Indications: *see notes above*

Cautions: insulinoma, starvation and adrenal insufficiency; ineffective in chronic hypoglycaemia

Contraindications:
phaeochromocytoma

Side-effects: nausea, vomiting, diarrhoea; rarely hypersensitivity

Dose: *by intramuscularly, intravenously or subcutaneously*, for adult and child over 25 kg, 1 mg (1 unit); child under 25 kg, 0.5 unit.

Note. I unit of glucagons = 1 mg of glucagon or glucagon hydrochloride

Generic Preparation
Injection: powder for reconstitution, glucagon as hydrochloride with lactose, 1 mg (=1 unit)/ vial; 1mg/ml/vial.

5.2.4 DRUGS USED IN DIABETIC NEUROPATHY

In case of painful diabetic neuropathy, optimal control is essential. Patients should be treated with insulin and relief can be probably accelerated by continuous insulin infusion. **Aspirin** and **paracetamol** (non-opioids analgesics) are indicated for pain. (**Tricyclic antidepressants like Amitriptyline, Imipramine, Nortriptyline**) are also recommended for the relief of pain**. Duloxetine** is effective for the treatment of
painful diabetic neuropathy. If treatment with
amitriptyline or duloxetine is inadequate, treatment with
Pregabalin should be tried. **Gabapentin** and **Carbamazepine** are sometimes used for the treatment of neuropathic pain.*(see section 7.6)*

In autonomic neuropathy diabetic, diarrhoea can be controlled by 2 or 3

doses of **Tetracycline** 250 mg. Antiemetics may control vomiting in gastroparesis. In neuropathic postural hypotension an increased salt intake and the use of the mineralocorticoid **Fludrocortisone** 100 to 400 microgram daily help by increasing plasma volume but edema is a common side-effect. Gustatory sweating can be managed by antimuscarinics e.g. **Propantheline bromide** *(see section 2.3.2).*

DULOXETINE

Indications: major depressive disorder, generalized anxiety disorder, osteoarthiritis, painful peripheral neuropathy, particularly diabetic neuropathy, to control the symptoms of fibromyalgia.

Cautions: increase the risk of suicide in persons younger than 25.

Contraindications: children and adolescents and in the 18–24 age group.

Side-effects: nausea, somnolence, insomnia, dizziness

Dose: diabetic neuropathy, ADULT over 18 years, 60mg once daily; max. 120mg daily in divided doses

Proprietary Preparations

Diliner *(Square),* DR Cap., 30 mg, Tk. 10.04/Cap.; DR Cap.,60 mg, Tk. 16.06/Cap.
Dulox *(Acme),* Tab., 20 mg, Tk.7.02/Tab.; 30mg, Tk. 10.04/Tab.
Duloxen *(Incepta),* Tab., 20 mg, Tk. 7.00/Tab.; Tab., 30 mg, Tk. 10.00/Tab.
Duzela *(Sun),* Cap., 20 mg, Tk. 7.05/Cap.
Stresin *(Unimed),* Cap., 20 mg, Tk. 8.00/Cap.
Xinolax*(Opsonin),* DR Cap., 20 mg, Tk. 5.26/Cap.;DR Cap., 30 mg, Tk. 7.52/Cap.;DR Cap., 60 mg, Tk. 12.03/Cap**.**

5.3 ADRENOCORTCALSTEROIDS

5.3.1 Replacement therapy
5.3.2 Glucocorticoid therapy

5.3.1 REPLACEMENT THERAPY

The adrenal cortex secretes hydrocortisone (cortisol) which is predominantly a glucocorticoid with weak mineralocorticoid activity. It also secretes aldosterone, a potent mineralocorticoid hormone. Physiological replacement in deficiency state is best achieved by a combination of **hydrocortisone** and the mineralocorticoid **fludrocortisone**; hydrocortisone alone usually does not provide sufficient mineralocorticoid activity for complete replacement. In Addison's disease or following bilateral adrenalectomy, hydrocortisone 20–30 mg daily by mouth is usually required. This is given in 2 divided doses, 2/3rd in the morning and rest in the evening; mimicking the normal diurnal rhythm of cortisol secretion. The optimal daily dose is determined on the basis of clinical response. Glucocorticoid therapy is supplemented by fludrocortisone 50–300 micrograms daily. In acute adrenocortical insufficiency, hydrocortisone is given intravenously, (preferably as sodium succinate) in doses of 100 mg every 6–8 hourly in sodium chloride (0.9%) intravenous infusion. Glucocorticoids should be given in hypopituitarism as in adrenocortical insufficiency, but since the production of aldosterone is also regulated by the renin-angiotensin system, a mineralocorticoid is not usually required. Additional replacement therapy with thyroxine and sex hormones should be given as indicated by the hormone deficiency.

Corticosteroid cover for adrenalectomy, for hypophysectomy or for operations on patients on long term treatment with steroids is determined from the knowledge that normally a person in major stress will not secrete more than 300 mg of cortisol in 24 hours; once the stress is over, return to maintenance dose (approximately 20 mg per 24 hours) gradually. For example: an operation under steroid coverage can be done by one injection of 100 mg hydrocortisone given intramuscularly or intravenously as a premedication, and then repeated 8 hourly. In absence of complications, the dose can be halved every 24 hours until a maintenance dose of 20–30 mg per day is reached on the 5th day after the operation.

5.3.2 GLUCOCORTICOID THERAPY

Mineralocorticoid effects of **Cortisone** and **Hydrocortisone** are too high to be used on long-term basis for suppression of inflammation; fluid retention will be too great, but they are suitable adrenal replacement therapy. Hydrocortisone is preferred because cortisone is only active after conversion in the liver to hydrocortisone. Used on a short-term basis, hydrocortisone is given by intravenous route during emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a first choice topical corticosteroid for the management of inflammatory skin conditions; cortisone is not active topically. **Prednisolone** has predominantly glucocorticoid activity and is most commonly used by mouth for long-term disease suppression. **Prednisone** has similar level of glucocorticoid activity but is only active after conversion in the liver to prednisolone; it is not recommended. **Betamethasone** and **dexamethasone** have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high dose therapy such as in cerebral edema. They have long duration of action; so they are suitable for conditions which require suppression of ACTH secretion (e.g. congenital adrenal hyperplasia). Some esters of betamethasone and of **Beclomethasone** have a marked topical effect (e.g. on the skin or the lungs) than when given orally. Such topical effect without much systemic activity is useful for skin applications and asthma inhalations. **Deflazacort** is a newly introduced corticosteroid with high glucocorticoid activity; it is derived from prednisolone.

Disadvantage of Corticosteroids. Prolonged use or overdosage may exagg-erate some of the actions of corticosteroids leading to mineralocorticoid and glucocorticoid side-effects. **Mineralo-corticoid side-effects** include hyperten-sion, sodium and water retention and hypokalemia. These are more marked in fludrocortisone, but are also significant with cortisone, hydrocortisone, corticotropin and tetracosactrin. Negligible mineralocorticoid side-effects occur with dexamethasone and betamethasone, and only slightly occur with prednisolone, prednisone, methylprednisolone and triamcinolone. **Glucocorticoid side-effects** include diabetes mellitus, osteoporosis, muscle wasting, peptic ulcer, mental disturbances like euphoria, paranoid state or depression. In children, there may be growth suppression. During pregnancy high dose can affect foetal adrenal development. High doses may cause exogenous Cushing's syndrome and suppression of pituitary—adrenal axis leading to secondary adrenal insufficiency and atrophy. This atrophy may persist for years, requiring steroid coverage during any illness or surgical emergency.

Clinical uses of corticosteroids. Dosage of corticosteroids varies widely in different diseases and in different indivi-duals. If the use of a corticosteroid can save or prolong life (as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection), high doses may need to be given, as the complications of therapy are likely to be less serious than the effect of the disease itself. Long-term therapy is required for chronic diseases (e.g. rheumatoid arthritis), and in that case the complications of therapy may become more serious than the disease. To minimize side-effects, the maintenance dose should be as low as possible. **Fludrocortisone** is used for the treatment of postural hypotension in autonomic neuropathy.

Corticosteroids are used rectally, by mouth or intravenously in the management of ulcerative colitis and Crohn's disease. Very high doses of corticosteroids have been given by intravenous injection in septic shock. Lack of marked mineralocorticoid action and their long term action make

Dexamethasone and **Betamethasone** particularly suitable for suppressing corticotrophin secretion in congenital adrenal hyperplasia where the dose should be tailored to clinical response and by measurement of adrenal androgens and 17 hydroxyprogesterone. In common with all glucocorticoids their suppressive action on the hypothalamo-pituiotary adrenal axis is greatest and most prolonged when they are given at night. Dexamethasone and betametha-sone are also appropriate for conditions where water retention would be a disadvantage (e.g. in cerebral edema) with doses of 12 to 20 mg daily.

In acute hypersensitive reactions like angiedema of upper respiratory tract or anaphylactic shock, corticosteroids are indicated as adjunct to emergency treatment with adrenaline. In such case hydrocortisone by intravenous injection in a dose of 100 to 300 mg may be required. Corticosteroids are used by inhalation in the management of asthma but systemic therapy in association with bronchodilators are required for the management of severe acute asthma. Corticosteroids are also useful in conditions such as rheumatic fever, chronic active hepatitis and sarcoidosis; they may also lead to remissions of acquired haemolytic anemia, and some cases of nephrotic syndrome and thrombocytopenic purpura. Corticoste-roids can improve the prognosis of serious conditions such as systemic lupus erythematosus (SLE), temporal arteritis and polyarteritis nodosa; the effects of the disease process may be suppressed and symptoms relieved, but the underlying condition is not cured, although it may ultimately burn itself out.

In non-expert hands, corticosteroids can often be misused, sometimes leading to serious consequence for the patients. Unless it is life-saving or very essential, long-term use should be avoided. Whenever possible, local treatment with creams, intra-articular injection, inhalations, eye-drops, or enemas should be used in preference to systemic treatment. The suppressive action of corticosteroid on cortisol secretion is least when it is given in the morning; therefore whenever possible single morning dose of steroid is preferred. For special safety precautions during pregnancy and breast- feeding, *see Appendix-5 & 6.*

BECLOMETHASONE DIPROPIONATE

Indications: chronic bronchial asthma not controlled by short-acting beta$_2$ agonists *(see also section 4.2)*

Cautions: active or quiescent tuberculosis; systemic therapy may be required during periods of stress or airways obstruction or mucus preventing drug access to smaller air way

The possibility of *paradoxical bronchospasm* should be borne in mind. The drug should be discontinued and alternative therapy started. If it is mild it may be prevented by inhalation of beta$_2$ agonist or by transfer from an aerosol inhalation to a dry powder inhalation

Side effects: *see also section 4.2.* It can cause candidiasis which can be prevented by using spacer. It also responds to antifungal lozenges after inhalation of a dose. There may not be any need to discontinue the therapy

Dose & Preparations: *see section 4.2*

BETAMETHASONE [ED]

Indications: suppression of inflammatory and allergic disorders, congenital adrenal hyperplasia, cerebral edema; *see notes above and ear (sec.11.1), eye (sec 10), nose (sec11.2) and skin (sec. 12)*

Cautions; Contraindications; Side-effects: *see notes above and under prednisolone*

Interactions: *see Appendix-2*

Dose: *by mouth*, usual range 0.5-5 mg/day

by intramuscular injection or slow intravenous injection or infusion, 4–8 mg, repeat up to 4 times in 24 hours; for

CHILD: by slow intravenous injection, up to 1 year 1 mg, 1–5 years 2 mg, 6–12 years 4 mg

Proprietary Preparations
Bet-A *(Acme),* Tab., 0.50 mg, Tk. 0.72/Tab
Betnelan *(GSK),* Tab., 0.5 mg, Tk. 0.63/Tab.

DEFLAZACORT

Indications: used as an immuno-suppressant.
Cautions: history of adrenal suppression, infections (ex- chickenpox, shingles, measles) children, elderly, tuberculosis, recent heart attack,
Contraindications: renal impairment, pregnancy and breast feeding, active thyroid, osteoporosis, diabetes mellitus
Side effects: impaired glucose tolerance, weight gain, abdominal bloating, nausea, muscle weakness, change in pigmentation, increased hair growth, mood changes
Dose: ADULT: Initially up to 120 mg/day.maintenance: 3-18 mg/day. CHILD: oral: 0.25-1.5 mg/kg/day given on alternate days. Suspension: 5 ml – 60 ml per day.

Proprietary Preparations
Deflacort *(Square),* Tab., 6 mg, Tk. 8.00/Tab.
Xalcort *(Beacon),* Tab., 6 mg, Tk. 8.00/Tab.

DEXAMETHASONE [ED]

Indications: suppression of inflammatory and allergic disorders; shock; diagnosis of Cushing's syndrome; congenital adrenal hyperplasia; cerebral edema; rheumatic disorders
Cautions; Contraindications; Side-effects: *see notes above and under prednisolone;*
Interactions: *see Appendix-2*
Dose: *by mouth*, usual range 0.5-10 mg/day; *by intramuscular injection or slow intravenous injection or infusion* (as with dexamethasone phosphate), initially 0.5–20 mg; for CHILD: 200–500 micrograms/kg daily. For cerebral edema (as dexamethasone phosp-hate),*by intravenous injection,* 10 mg initially, then 4 mg intramuscularly once every 6 hours as required for 2–10 days

Proprietary Preparations
Amason *(Ambee),* Tab., 0.5 mg , Tk 1/ Tab
D-cort *(Globe),* Tab., 0.50 mg, Tk. 0.75/Tab.; Inj., 5 mg /ml, Tk. 15.00/Amp.
Decafos *(Techno),* Tab., 0.5 mg, Tk. 0.38/Tab.; Inj, 5 mg/1 ml , Tk. 17.00/Amp.
Decason *(Opsonin),* Inj., 5 mg/1 ml, Tk. 16.66/Amp.;Tab., 0.5 mg, Tk. 0.75/Tab.
Dexa *(Renata),* Tab. , 0.5 mg, Tk. 0.75/Tab.; Inj, 5 mg/1 ml , Tk. 25.00/Amp.
Dexagen *(General),* Inj, 5 mg/1 ml, Tk. 22.00/Amp.;Tab. , 0.5 mg, Tk. 1.00/Tab.
Dexam *(Medimet),* Inj., 0.05mg/Amp., Tk.15.00/Amp.; Tab., 0.05mg, Tk.1.00/Tab.
Dexamet *(Rephco),* Inj, 5 mg/1 ml , Tk. 16.00/Amp.;Tab. , 0.5 mg, Tk. 0.70/Tab.
Dexamethasone *(Albion),* Tab. , 0.5 mg, Tk. 1.00/Tab.
Dexamethasone*(APC),* Tab., 0.5 mg, Tk. 0.42/Tab.
Dexamin *(Jayson),* Inj, 5 mg/1 ml, Tk. 18.00/Amp. Tab. , 0.5 mg, Tk. 0.55/Tab.
Dexan *(Chemist),* Tab., 0.5 mg, Tk. 0.42/Tab.;; Inj., 5 mg, Tk. 15.00/1 ml Amp.
Dexon *(Ibn Sina),* Inj, 5 mg/1 ml, Tk. 16/Amp.
Dexonex *(Square),* Inj, 5 mg / 5 ml, Tk. 20.00/Amp. ;Tab. , 0.5 mg, Tk. 0.89/Tab.
Dextason *(Ziska),* Inj., 5mg/1ml, Tk. 12.00/1ml Amp.; Tab., 0.5mg, Tk. 0.60/Tab.
Dextor *(Eskayef),* Tab, 0.5 mg, Tk. 1.00/Tab.
G-Dexamethasone *(Gonoshasthaya),* Inj, 4mg/ ml, Tk. 10.00/Amp
Gludex *(Kemiko),* Inj, 5 mg/1 ml , Tk. 22.00/Amp. ;Tab. , 0.5 mg, Tk. 1.00/Tab.
Odeson *(Beximco),* Inj, 4 mg/ ml, Tk. 15/Amp.
Sonexa *(Aristo),* Inj, 5 mg/1 ml, Tk. 15/Amp.
Stedex *(Navana),* Inj, 5 mg/1 ml, Tk. 22/Amp
Steron *(Acme),* Inj, 5 mg/1 ml , Tk. 22.00/Amp. ;Tab. 0.5mg, Tk. 0.9/Tab**.**

HYDROCORTISONE [ED]

Indications: adrenocortical insufficiency; shock; hypersensitivity reactions (such as anaphylactic shock, angioedema), inflammatory bowel disease, rheumatic disease, eye disease, skin disease *(see sections 10 & 11)*
Cautions; Contraindications & Side-effects: *see notes above and under Prednisolone*
Interactions: *see Appendix-2*
Dose: *by mouth*, replacement therapy, 20-30 mg/day in divided doses. For CHILD: 10-30 mg/day. *By Intramuscular*

injection or slow intravenous injection or infusion, 100–500 mg, 3–4 times in 24 hours or as required; in CHILD: *by slow intravenous injection* up to 1 year 25 mg, 1-5 years 50 mg, 6–12 years 100 mg

Proprietary Preparations
Anacort *(Techno),* Inj.,100 mg/vial,Tk. 60/Vial
Cortef *(Aristo),* Inj., 100 mg/vial, Tk. 50/Vial
Cortimet *(Medimet),* Cream, 1gm,Tk.28/10 gm
Cortinex *(Ziska),* inj., 100 mg/Vial, Tk. 50/Vial
Cotson *(Opsonin),*Inj.,100 mg/vial, Tk. 37.74/Vial
Glucort *(Globe),* Inj., 100 mg/Vial, Tk. 50/Vial
Hison *(ACI),* Inj., 100 mg/vial, Tk. 50.19/Vial
Hycort *(Chemist),* Inj., 100 mg/Vial, Tk. 50/Vial
Intasone *(Incepta),*Inj.,100 mg/vial, Tk. 50/Vial

METHYLPREDNISOLONE

Indications: suppression of inflammatory and allergic disorders; cerebral edema; rheumatic disorders *(see sec. 9.1.2.1)*, skin diseases *(see section 12)*
Cautions; Contraindications & Side-effects: *see notes above and under Prednisolone;* rapid intravenous administration of large dose has been associated with cardiovascular collapse
Interactions: *see Appendix-2*
Dose: *by mouth*, usual range 2-40 mg/day, for chemotherapy emesis. *By intramuscular injection or slow intravenous injection or infusion* (as dexamethasone phosphate), initially 10-100 mg; graft rejection up to 1 g/day by infusion for up to 3 days

Proprietary Preparations
Methipred *(General),* Tab., 16 mg, Tk. 20.00/Tab.*;* 2 mg, Tk. 3.00/Tab.; 4 mg, Tk. 5.00/Tab.;8 mg, Tk. 10.00/Tab.
Predixa *(Unimed),* Tab. , 16 mg, Tk. 24.00/Tab.; 4 mg, Tk. 6.00/Tab.
Solupred *(Ziska),* Tab., 4mg, Tk. 5.00/Tab.; 16mg, Tk. 15.00/Tab.

Methylprednisolone Acetate
Depodrol *(Opsonin),* Inj., 40 mg/vial, Tk. 48.87/Vial
Depomed *(Drug Int),* Inj., 40 mg/vial, Tk. 75.00/Vial ; 80 mg/vial, Tk. 100.00/Vial
Depo-pred *(Ziska),* Inj., 40mg/ml, Tk. 75.00/ml Vial
Medrol *(Techno),* Inj., 40 mg/vial, Tk. 65.00/Vial ; 80 mg/vial, Tk. 90.00/Vial
Mepcort *(Globe),* Inj., 1 gm, Tk. 1000.00/Vial; 500 mg, Tk. 600.00/Vial
Uni-medrol *(Chemist),* Inj., 40mg/1ml, Tk. 65.00/1 ml Vial; 80mg/2ml, Tk. 90.00/2 ml Vial

Methylprednisolone (as Sodium Succinate)
Pro-Medrol *(Techno),* Inj., 1 gm/Vial, Tk. 1,200.00/Vial; 500 mg/Vial, Tk. 800.00/Vial
Solupred *(Ziska),* Inj., 125 mg/Vial, Tk. 200.00/Vial; 1g/Vial, Tk. 1000.00/Vial; 500mg/Vial, Tk. 600.00/Vial

PREDNISOLONE [ED]

Indications: suppression of inflammatory and allergic disorders, inflammatory bowel disease, asthma, immunosuppression, rheumatic disease *(sec 9.1.2.1)*; *see notes above and also sub-sections on ear (sec.11.1), eye (sec 10), nose (sec11.2) and skin (sec 11.2)*
Cautions: adrenal suppression, infection, children and adolescents (growth retardation); elderly frequent monitoring required in those with history of tuberculosis, hypertension, recent myocardial infarction, congestive heart failure, liver failure, renal impairment, diabetes mellitus, osteoporosis, glaucoma, severe affective disorders, epilepsy, peptic ulceration, hypopituitarism, history of steroid myopathy; pregnancy and breastfeeding.
Adrenal suppression: prolonged therapy with prednisolone may cause adrenal atrophy which may persist for years after withdrawal of the drug. Too rapid reduction of dose after prolonged course (more than 7 days) can lead to adrenal crisis (shock). So withdrawal should be gradual-over weeks or even months, depending on dose and duration of therapy. Withdrawal may also be associated with fever, myalgia, arthalgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight. Any significant intercurrent illness, traumas, or surgical procedures requires a temporary increase in dosage, or if already stopped, a temporary re-introduction of corticosteroids. Patients on steroid therapy should carry a treatment card giving clear instructions on precautions to be taken to minimize risk and provide details of drug, dose

and duration of treatment. Anaesthetists must know whether a patient is taking or has been taking corticosteroids to avoid precipitious fall of blood pressure during anaesthesia or in the immediate post-operative period

Infections: susceptibility and severity of infections may be increased and clinical presentation may be atypical. Serious infections e.g. septicaemia and tuberculosis may reach an advanced stage before being recognized. Symptoms of amoebiasis, strongyloidiasis, measles and chickenpox may exacerbate if corticosteroids are being taken by the patients simultaneously

Contraindications: systemic infection (until specific treatment is given); avoid live virus vaccines in those receiving immunosuppressive doses

Side-effects: use of lowest effective dose can minimize side-effects. Gastrointestinal effects include dyspepsia, peptic ulceration (with perforation), abdominal distension, acute pancreatitis, oesophagial ulceration and candidiasis. Musculoskeletal effects include proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture. Endocrine effects include adrenal suppression, menstrual irregularities and amenorrhoea. Cushing's syndrome (with high dose), hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite. Neuropsychiatric effects include euphoria, dependence, depression, insomnia, increased intracranial pressure with papilledema in children, psychosis and aggravation of schizophrenia, suicidal tendencies, aggravation of epilepsy. Ophthalmic effects include glaucoma, papilledema, posterior sub-capsular cataract, corneal or scleral thinning and exacerbation of viral or fungal eye disease. Other side-effects include impaired healing, skin atrophy, bruise, striae, telengiectasia, acne, myocardial rupture following recent myocardial infarction, fluid and electrolyte imbalance, leukocytosis, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, hiccup and malaise

Interactions: *see Appendix-2 (corticosteroids)*

Dose: *by mouth*, up to 10-20 mg/day (severe disease, up to 60 mg/day), preferably taken in the morning after breakfast; can often be reduced within few days but may need to be continued for several weeks or months. For maintenance, usual range 2.5–15 mg/day, but higher dose may be needed; Cushingoid side-effects are likely with dose above 7.5 mg/day

by intramuscular injection, prednisolone acetate, 25–100 mg once or twice weekly

Proprietary Preparations

Altason *(Albion),* Tab., 10 mg, Tk. 2.07/Tab.; Tab., 20 mg, Tk. 3.73/Tab.; Tab., 5 mg, Tk. 1.14/Tab.

Bexipred *(Beximco),* Tab. , 20 mg, Tk. 6.27/Tab.

Cortan *(Incepta),* Tab. , 10 mg, Tk. 3.23/Tab.; Tab., 20 mg, Tk. 6.27/Tab. ;Tab. , 5 mg, Tk. 1.72/Tab.;

Cortisol *(Aristo),* Tab. , 5 mg, Tk. 1.70/Tab. ; 20 mg, Tk. 6.25/Tab. ; 10 mg, Tk. 3.20/Tab. ; Syrup 5 mg/5 ml, 5 mg/5 ml, Tk. 65.00/50 ml

Deltapred *(Ziska),* Tab., 10mg, Tk. 2/Tab.; 20mg, Tk. 3.75/Tab.; 5mg, Tk. 1.10/Tab.

Deltasone *(Renata),* Tab. , 10 mg, Tk. 2.07/Tab. ; 20 mg, Tk. 3.73/Tab. ;Tab. , 5 mg, Tk. 1.14/Tab.Syrup 5 mg/5 ml, Tk. 60.00/50 ml; Tk.95.00/100ml

G-Prednisolone *(Gonoshasthaya),* Tab. , 5 mg, Tk.1.14/Tab.

Inflagic *(Square),* Tab., 5 mg, Tk. 1.15/Tab.; 20 mg, Tk. 3.98/Tab.

P-cort *(Globe),* Solu, 5 mg/5 ml, Tk. 60/50ml

Pedipred *(Ziska),* Solu, 5mg/5ml, Tk. 95/100ml; Tk. 60/50ml

Pedlon *(MST),* Tab., 10 mg, Tk. 2/Tab.; 20mg, Tk. 3.75/Tab; Oral Solu, 135 mg/100 ml, Tk. 95/100 ml; 60 / 50 ml

Precodil *(Opsonin),* Tab., 10 mg, Tk. 2.43/Tab20 mg, Tk. 4.71/Tab.; 5 mg, Tk. 0.86/Tab.

Pred *(Eskayef),* Tab, 5 mg, Tk. 1.14/Tab.;20 mg, Tk. 3.70/Tab.;10 mg, Tk. 2.00/Tab.

Prednelan*(GSK),* Tab. , 20 mg, Tk. 281.97/Tab. ;Tab. , 5 mg, Tk. 1.50/Tab.

Prednisolone *(Ambee),* Tab., 5 mg, Tk. 1.2/Tab. Syrup 5 mg/5 ml, Tk. 95.00/100 ml ; Tk. 60.00/50 ml; Syrup, 15 mg/5 ml, Tk. 60.38/50 ml; Tk. 98.11/100 ml; 5 mg/5 ml, Tk. 55/100 ml; Tk. 48.87/50 ml

TRIAMCINOLONE

Indications: suppression of inflammatory and allergic disorders; rheumatic disorders *(section 9.1.2.1),* mouth and skin diseases *(sections 11.2.1 & 12.3)*
Cautions; Contraindications & Side-effects: *see notes above and under Prednisolone;* triamcinolone in high dosage has a greater tendency to cause proximal myopathy and should be avoided in chronic therapy
Interactions: *see Appendix-2.*
Dose: *by mouth*, usual range 2-24 mg/day. *By deep intramuscular injection*, 40 mg of acetonide for depot effect, repeated at intervals according to patient's response; maximum single dose 100 mg

Proprietary Preparations
Alfacort *(Ziska),* Inj., 40 mg/ml, Tk.15/1ml Vial
Cenolon *(Incepta),* Inj., 40 mg/vial, Tk. 75/Vial
Cynocort *(Techno),* Inj., 40 mg/vial,Tk. 60/Vial
Trecilon *(Rephco),* Inj., 40 mg/vial, Tk. 65/Vial
Triacin *(Kemiko),* Inj., 40 mg/vial, Tk. 60/Vial
Trialon *(Drug Int.),* Inj., 40 mg/vial, Tk. 75/Vial;
Triamon *(Globe),* Inj.,40 mg/ml,Tk.70/1ml amp
Trimcort *(Chemist),* Inj., 1 ml, Tk. 60/1 ml Vial; Oral Pest, 10 gm, Tk. 100/10 gm

5.4 SEX HORMONES

5.4.1 FEMALE SEX HORMONES AND ANTAGONISTS

5.4.1.1 OESTROGENS AND HORMONE REPLACEMENT THERAPY (HRT)

Oestrogens are necessary for puberty development in female; they also stimulate myometrial hypertrophy with endometrial hyperplasia. **Natural oestrogens** (oestradiol, oestrone and oestriol) have more appropriate profile in terms of oestrogenic activity than **synthetic oestrogens** (ethinyloestradiol, mestranol, stilboesterol) for hormone replacement therapy (HRT). The activity of **conjugated oestrogens** resemble that of natural oestrogens.
Oestrogen therapy is given cyclically or continuously for a number of gynaecological conditions. During long term treatment a progestogen should be added to prevent cystic hyperplasia of endometrium and possible transformation to cancer. Oestrogens are no longer used to suppress lactation because of their association with thromboembolism.
Hormone Replacement Therapy (HRT)
Hormone replacement therapy is indicated for menopausal women to relieve the inconveniences due to vaginal atrophy or vasomotor instability. Oestrgens relieve vasomotor symptoms, prevent bone loss, promote new bone formation, restore normal urogenital and skin epithelium, reduce incidence of stroke and myocardial infarction. Only small dose oestrogens are used for HRT, either alone or in combination with progestogens. A woman with uterus requires oestrogen with cyclical progestogen for the last 10-14 days of the cycle or administration of a preparation which combines both oestrogenic and progestogenic activity. Oestrogen therapy alone is suitable for long-term continuous therapy in a woman without a uterus. Cyclical HRT (where a progestogen is taken for 10-14 days of each cycle) usually results in a regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken continuously) is to avoid withdrawal bleeding but irregular bleeding may occur during early treatment stages; if it continues, endometrial abnormality needs to be excluded and cyclical HRT considered.
With HRT, there is an increased risk of endometrial cancer, which can be reduced by combining progestogens along with oestrogens. After prolonged use for some years, there may be an

increased risk of breast cancer. Recent studies indicate an increased risk of deep vein thrombosis and of pulmonary embolism in women taking HRT. Being beneficial for most menopausal women, HRT may be prescribed if not specifically contraindicated. HRT should be undertaken only under specialist supervision.

Side-effects of HRT include nausea, vomiting, breast enlargement and tenderness, premenustrual-like syndrome, fluid retention, change in liver function, cholestetic jaundice, rashes and chloasma, depression, migraine or migraine like headache. Transdermal delivery system may cause contact sensation (possible severe hypersensitivity reaction on continued exposure).

Contraindication of HRT: Oestrogen dependent neoplasm (oestrogen receptor positive); active thromboembolism; liver diseases, Dubin-Janson and Rotor syndrome; undiagnosed abnormal genital bleeding.

Choice of Preparation: Many proprietary single or combination preparations for HRT are available in the international market but only a few of them are available in Bangladesh now. Some of the preparations available in Bangladesh are listed below. For doses and instructions , *see manufacturers' literature and inserts.*

Proprietary Preparations

Preampak-C[I] *(Ayrest),*Tab.conjugated oestrogen 625 microgram and norgestrel 150 microgram.Tk.12.33/Tab
Pausogest[I] *(Richter),*Tab.estradio2mg and Norethisteron 1mg Tk.25.22/Tab.
Estrimox[I] *(Richter),* Tab. estradiol 2mg Tk.417.23/28's Tab

Conjugated oestragens only
Estracon *(Renata),*Tab., 0.625mg, Tk. 20/Tab.
Premicon *(Techno),*Tab., 0.625mg, Tk.15/Tab
Premarin [I]*(Ayrest)*, Tab. 0.625mg, Tk.29.85/Tab

ETHINYLOESTRADIOL

(Other name: Ethinylestradiol)

Indications: used as hormone replacement in menopause in a dose of 10-20 micrograms daily. This has now been largely replaced by more suitable forms of oestrogen. It is also used in breast cancer
Cautions; Contraindications; Side-effects: cardiovascular disease and hepatic impairment
Interactions: *see appendix-2*
Dose: *see indications above*

Generic Preparation

Tablets, 10 micrograms; 50 micrograms

OESTRIOL

Oestriol is a naturally occurring oestrogen with actions similar to other oestrogenic hormones.
Indications: treatment of and prophylaxis of menopausal disorders. It has also been given in combination with other natural oestrogens in HRT *(see notes above)*
Cautions, Contraindications: pregnancy, thrombosis, oestrogen dependent tumours, undiagnosed vaginal bleeding
Interactions:*see Appendix-2*
Side-effects: pain in breast, spotting or excessive cervical exudation (reduce dose), nausea
Doses: for short-term treatment orally 500 micrograms to 3 mg daily as single dose for one month and then reduced to 500 micrograms to 1 mg daily; usual doses range from 250 micrograms to 2 mg daily

Proprietary Preparations

Defogen *(Incepta),* Tab., 1 mg , Tk. 8.00/Tab.
Femastin *(Square),* Tab., 1 mg, Tk. 8.00/Tab.
Ovestin *(Nuvista),* Tab. 1mg Tk. 9.90/Tab.;
Ovestin[I]*(Organon)* Cream 1 mg/g; Tk. 240.05/15g

TIBOLONE

Tibolone (a synthetic steroid structurally related to norethinodrel) combines oestrogenic and progestogenic activity with weak androgenic activity.
Indications: teatment of vasomotor symptoms in oestrogen deficiency

menopausal women (including women being treated with gonadotrophin releasing hormone analogues), osteoporosis pro-phylaxis and HRT. Tibolone is now popular for HRT because no withdrawal bleeding occurs if it is started after one year of spontaneous menopause
Cautions: renal insufficiency, epilepsy, migraine, diabetes, hypercholesterolemia, abnormal liver function tests, thrombophlebitis, thromboembolism, pregnancy, breast-feeding, uninvesti-gated vaginal bleeding
Contraindications: hormone depen-dent neoplasm; active thromboembo-lism; liver diseases, undiagnosed abnormal genital bleeding
Interactions: *see Appendix-2*
Side-effects: weight change, ankle edema, seborrhoeic dermatitis, vaginal bleeding, gastrointestinal disturbance, headache, increased facial hairs, migraine, visual disturbance, liver function test abnormality; rash and pruritus has also been reported
Dose : 2.5 mg daily continuous

Proprietary Preparations
Menorest *(Renata),* Tab., 2.5 mg, Tk. 20.07/Tab.
Renorma *(Square),* Tab., 2.5 mg, Tk. 20.07/Tab.
Tibo*(Popular),* Tab., 2.5 mg, Tk. 20.08/Tab.
Tibon *(Techno),* Tab., 2.5 mg, Tk. 15.00/Tab.
Tibonor *(Eskayef),* Tab., 2.5 mg, Tk. 20.00/Tab.
Tivion *(ACI),* Tab., 2.5 mg, Tk. 20.00/Tab.
Ubilon *(Incepta),* Tab., 2.5 mg, Tk. 20.00/Tab.

5.4.1.2 PROGESTOGENS

There are two main groups of progestogen-progesterone and its analogues (dydrogestenone, hydroxypr-ogesterone, medroxyprogesterone); and testosterone analogues (norethisterone and norgestrel). The newer progest-ogens (desogestrel, norgestimate, and gestodene) are derivative of norgestrel; levonorgestrel is the active isomer of norgestrel and has twice its potency. Progesterone and its analogues are less androgenic than the testosterone derivatives; neither progesterone nor dydrogesterone causes virilisation. Other synthetic derivatives are variably metabolised into testosterone and oestrogen; thus side-effects vary with preparations and the dose. Some progestogens such as norethisterone are used in endometriosis.
Oral progestogens are used widely for menorrhagia but they are relatively ineffective compared to other agents. Oral progestogens are also used for severe dysmenorrhea, but in young women where contraceptive is also necessary, best choice is combined oral contraceptives. Progestogens are used for alleviation of premenstrual symptoms, but no convincing physiological basis for treatment has been shown. Progestogens have been used in habitual abortion but there is no evidence of benefit; if they are used for this purpose they should be of true progesterone derivatives (e.g. hydroxyp-rogesterone hexanoate) to avoid possible musculinisation of female fetus. In post-menopausal women receiving long-term oestrogen therapy for hormone replacement, a progestogen needs to be added to prevent cystic hyperplasia of the endometrium and possible transformation to cancer. **Desogestrel, ethynodiol, gestodene, levonorgestrel, norethisterone and norgestimate** are used in combined oral contraceptives and in progestogen only contracep-tives *(see section 6.3.2.1).* Progestogens have no role in neoplastic disease.

DYDROGESTERONE

Indications: *se under dose and notes above*
Cautions; Contraindications & Side-effects: *see under* Medroxypro-gesterone *Acetate and notes above;* break-through bleeding may occur
Dose: edometriosis, 10 mg 2-3 times daily from 5th to 25th day of cycle or continuously; dysfunctional uterine bleeding, 10 mg twice daily (together with an oestrogen) for 5–7 days to arrest bleeding, and 10 mg (together with an

oestrogen) from 11th to 25th day of cycle to prevent bleeding; dysmenorrhoea *(see notes above)*, 10 mg twice daily from 5th to 25th day of cycle; amenorrhoea, 10 mg twice daily from 12th to 25th day of cycle with oestrogen therapy from 1st to 25th day of cycle; premenstrual syndrome (see notes above), 10 mg twice daily from 12th to 26th day of cycle increased if necessary; hormone replacement therapy, with continuous oetrogen therapy *(see section 7.5.1.1)*, 10 mg daily on days 15-28 of each 28-day oestrogen HRT cycle, increased to 10 mg twice daily if withdrawal bleeding is early or endometrial biopsy shows inadequate progestational response; habitual abortion *(see notes above)*, 10mg twice daily from 16th to 25th day of cycle until conception, then continuously until 20th weeks of gestation and gradually reduced

Proprietary Preparation
Duphaston[I] *(Abbott),* Tab. 10 mg. Tk.29.81/Tab

HYDROXYPROGESTERONE HEXANOATE

Indications: habitual abortion but *see note above.*
Cautions: pregnancy, diabetes.
Contraindications & Side-effects: *see under Medroxyprogesterone and notes above.*
Dose : *by slow intramuscular injection*, 250–500 mg weekly during first half of pregnancy.

Generic Preparation
Injection 250mg/ml;

LYNOESTRENOL

(Lynestrenol)

Indications: is a progestogen with actions and uses similar to those described for other progestogens. It has been used as an adjunct to oestrogen therapy in menopausal disorders. It is also used as the progestogenic component of some combined oral contraceptives or as a progestogen only contraceptive.
Cautions; Contraindications & Side-effects: as with other progestogens.

Proprietary Preparation
Orgatril *(Nuvista)*, Tab. 5mg, Tk. 11.55/Tab.

MEDROXYPROGESTERONE ACETATE

Indications: *see under dose,* contraception *(see section 6.3.2.1),* malignant disease *(see section 14.3.2).*
Cautions: diabetes, hypertension, cardiac or renal disease.
Interactions: *see Appendix -2.*
Contraindications: pregnancy, undiagnosed vaginal bleeding, active liver disease, breast or genital tract carcinoma.
Side-effects: gastrointestinal upset, change in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles, depression, insomnia, alopecia, hirsutism, anaphylectoid-like reactions, rarely jaundice
Dose: *by mouth*, 2.5–10 mg daily for 5-10 days beginning on 16th to 21st day of cycles, repeated for 2 cycles in dysfunctional uterine bleeding and 3 cycles in secondary amenorrhoea; mild to moderate endometriosis, 10 mg 3 times daily for 90 consecutive days beginning on 1st day of cycle. *By deep intramuscular injection (see section 6.3.2.2)*

Proprietary Preparations
see section 6.3.2.1

NORETHISTERONE

Indications: *see under dose,* HRT *(section 5.4.1.1)*; contraception *(section 6.3.2.1)*
Cautions; & Side-effects: *see under medroxyproges-terone acetate*,
Contraindications: pregnancy, epilepsy and migraine
Dose: endometriosis, 10 mg daily for 4-6 months or longer, starting on day 5 of cycle (increase the dose to 20–25 mg

daily if spotting occurs, reduce once bleeding stops); menorrhagia, 5 mg 3 times daily for 10 days to arrest bleeding, and to prevent bleeding 5 mg twice daily from 19th to 26th day of cycle; dysmenorrhoea, 5 mg 3 times daily from day 5 to 24 for 3-4 cycles; premenstrual syndrome, 5 mg 2 to 3 times daily from day 19 to 26 for several cycles; postponement of menstruation, 5 mg 3 times daily starting 3 days before anticipated onset (menstruation occurs 2-3 days after stopping); progestonic supplement to oestrogen in HRT *(see section 5.4.1.1)*

Proprietary Preparations
Ethinor *(Eskayef),* Tab., 5 mg, Tk.5.00/Tab.
Menogia *(ACI),* Tab., 5mg, Tk. 5.00/Tab.
Menoral *(Square),* Tab., 5 mg, Tk. 5.00/Tab.
Normens *(Renata),* Tab., 5 mg, Tk.5.02/Tab.
Noteron *(Incepta),* Tab.,5 mg, Tk.5.00/Tab.
Remens *(Popular),* Tab., 5mg, Tk. 5.00/Tab.

PROGESTERONE

Indications: *see under dose and notes above*
Contraindications: *see notes above*; missed or incomplete abortion
Side-effects: see notes above; injection site reaction; pain; diarrhoea and flatulence can occur with rectal administration
Dose: menopausal symptoms, insert 1 applicator of 4% gel on alternate days for the last 12 days of oestrogen therapy in each cycle.
Infertility due to inadequate luteal phase, insert 1 applicator of 8% gel daily starting either after documented ovulation or on day 18-21 of cycle In vitro fertilization, daily application of 8% gel, continued for 30 days after laboratory evidence of pregnancy.

Proprietary Preparations
Crinone[(I)] *(Merck),* Gel, 8%,Tk.304.32/1.45 gm
Microgest *(Renata),* Cap.,100 mg, Tk.15/Cap. 200 mg, Tk. 30/Cap.

5.4.2. ANTI-OESTROGENS

The anti-oestrogens **clomiphene** and **tamoxifen** are used in treatment of infertility due to ovulatory dysfunctions (as in polycystic ovarian syndrome). They induce gonadotropin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanism; chorionic gonadotropin is sometimes used as adjunct. Patient should be warned that there is risk of multiple pregnancy.

CLOMIPHENE CITRATE
(Clomifene Citrate)

Indications: anovulatory infertility, *see notes above.*
Cautions: polycystic ovary, ovarian hyperstimulation syndrome, uterine fibroids, ectopic pregnancy, multiple pregnancy, visual impairment.
Contraindications: hepatic disease, ovarian cysts, hormone dependent tumours, undiagnosed abnormal uterine bleeding, pregnancy.
Interactions: *see Appendix-2.*
Side-effects: visual disturbance, hot flushes, ovarian hyperstimulation, abdominal discomfort, nausea, vomiting, depression, insomnia, breast tenderness, headache, intermenstrual spotting, menorrhagia, endometriosis, convulsi-ons, weight gain, rashes, dizziness, hair loss
Dose: 50 mg daily for 5 days, starting within about 5 days of menstruation (preferably on 2nd day) or at any time (normally preceded by a progestogen-induced withdrawal bleeding) if no menses; second course of 100 mg daily for 5 days may be given if there is no ovulation; 3 courses should constitute adequate trial; long term cyclical therapy not recommended

Proprietary Preparations
Comipen *(Pacific),* Tab., 50 mg, Tk. 3.76/Tab.
Fermid*(Gaco*), Tab., 50 mg, Tk. 10/Tab
Fertil *(Beximco),* Tab., 50 mg, Tk. 10/Tab.
Ovuclon *(Incepta),* Tab., 100 mg, Tk. 18.00/Tab.;Tab., 50 mg, Tk. 10/Tab.

Ovulet *(Renata),* Tab., 100 mg, Tk. 18.06/Tab.; Tab., 50 mg, Tk. 10.04/Tab.
Reomen *(Eskayef),* Tab., 50mg, Tk. 10/Tab.

5.4.3 MALE SEX HORMONES AND ANTAGONISTS

Masculinisation is caused by androgens; they may be used as replacement therapy in adult with androgen deficiency due to pituitary or testicular disease or for castration. In normal males they inhibit gonadotropin secretion and thereby suppress spermatogenesis. Androgens also have anabolic action which led to the development of anabolic steroids *(see section 5.4.4).*
Treatment of impotence and impaired spermatogeneis by androgens is useless if there is associated hypogonadism. Androgen treatment in hypopituitarism can lead to normal sexual development and potency but not to fertility. When fertility is desired, gonadotropins or pulsatile gonadotropin releasing hormones therapy will stimulate spermatogenesis as well as androgen production. Induction of puberty in boys with delayed puberty by use of androgens or **chorionic gonadotropin** should be used with caution, and only under expert supervision.
Intramuscular depot preparations of **testosterone esters** are preferred for replacement therapy. Testosterone enanthate or propionate or a mixture of them has long duration of action. Menopausal women are also sometimes given implant of testosterone (in a dose 50-100 mg every 4–8 months) as an adjunct to hormone replacement therapy. Orally active preparations are **Testosterone undecanoate** and **mesterolone.**
Anti-androgens are used in the treatment of severe hypersexuality and sexual deviation in the male. **Cyproterone acetate** is an antiandro-gen; it inhibits spermatogenesis and produces reversible infertility but abnormal sperm forms are produced. Fully informed consent from the patient is recommended.

TESTOSTERONE AND ESTERS

Indications: testosterone replacement therapy in male hypogonadal disorders; osteoporosis due to androgen deficiency
Cautions: cardiac, renal or hepatic impairment; elderly, ischaemic heart disease, hypertension, epilepsy, migraine, skeletal metastasis (risk of hypercalcaemia), pre-pubertal boys (see notes above)
Contraindications: breast cancer in men, prostate cancer, hypercalcaemia, pregnancy, breast-feeding; nephrosis
Interactions: *see Appendix-2*
Side-effects: prostate abnormalities, prostate cancer, headache, depression, gastro-intestinal bleeding, nausea, cholestatic jaundice, change in libido, anxiety, generalized paraesthesia, electrolyte imbalance including sodium retention with edema and hypercalcemia; increase bone growth, androgenic effects such as hirsutism, male pattern baldness, seborrhoea, acne, excessive frequency and duration of penile erections, precocious sexual development and premature closure of epiphysis in prepubertal males, virilism in women, and suppression of spermatoge-nesis in men
Dos : *see under preparations*

Proprietary Preparations
Andriol [I] *(Organon),* Cap. Testosterone undeconate 40 mg,
Dose: initially 120-160 mg daily for 2-3 weeks, maintenance 40-120 mg daily. Tk. 672.00/tab

Testosterone Propionate 30mg, Testosterone phenylpropionate 60mg, Testosterone isocaproate 60mg, Testosterone decanoate 100 mg/ml
Testanon *(Nuvista),* Inj. Tk.161.70/1ml amp
Sustogen *(Techno),* Inj., Tk. 129.00/ml Amp.
Dose: For androgen deficiency, deep intramuscular injection 1 ml usually every 3 weeks .

ANTI-ANDROGENS

Cyproterone acetate is an antiandrogen used in the treatment of severe hypersexuality and sexual deviation in the male. It inhibits spermatogenesis and

produces reversible infertility but it is not used as male contraceptive; abnormal sperm forms are produced. Fully informed consent and an initial sperm count and morphology are recommended before anti-androgen therapy. Hepatic tumors have been reported in animals. Therefore, careful consideration should be given to the risk/benefit ratio before treatment. Cyproterone acetate is also used as an adjunct in prostatic cancer and in the treatment of acne and hirsutism in women.

Finasteride is a specific inhibitor of the enzyme 5-alpha-reductase which metabolises testesterone into the more potent androgen, dihydrotestesterone. This inhibition of testesterone metabolism reduces the prostate size with the improvement of the urinary flow rate and relieves obstructive symptoms. It is alternative to alpha-blockers particularly in men with a significantly enlarged prostate. A low strength of finasteride is used for treating male pattern baldness in men.

CYPROTERONE ACETATE

Indications: for the treatment of severe hypersexuality or sexual deviation in male; also used as an adjunct in prostate cancer and hirsutism in women (along with oestrogen)

Cautions: blood counts initially and throughout treatment; monitor hepatic function regularly. A semen analysis and fully informed consent from the patient is recommended

Contraindications: (do not apply in prostate cancer) hepatic disease, diabetes with vasculopathy; sickle cell anemia, malignant or wasting disease, severe depression, history of thromboembolic disorders; before 18 years of age (may arrest bone maturation and testicular development).

Interactions: *see Appendix-2*

Side-effects: fatigue, lassitude, breathlessness, weight changes, reduce sebum production, change in hair pattern, gynaecomastia (rarely galactorrhoea), osteoporosis, inhibition of spermatogenesis; hepatotoxicity (in high dose)

Dose: male hypersexuality, 50 mg twice daily after food

Generic Preparation

Tablet 50mg

FINASTERIDE

Indications: benign prostatic hyperplasia, male pattern baldness in men

Cautions: obstructive uropathy, prostate cancer (may decrease markers such as prostate specific antigen); use of condoms recommended if sexual partner is pregnant or is likely to become pregnant since finasteride is excreted in semen. It is not recommended in women of child bearing age

Side-effects: impotence, decreased libido, ejaculation disorders, testicular pain, breast tenderness and enlargement, hypersensitivity reactions such as pruritus, rashes, lip and face swelling

Dose: 5mg daily, treatment to be reviewed after 6 months; sometimes it may require several months to get benefit

Proprietary Preparations

Pronor *(Square),* Tab., 5 mg, Tk. 10.04/Tab.
Recur *(Beximco),* Tab., 1 mg, Tk. 4.02/Tab.; 5mg, Tk. 10.04/Tab.

5.4.4 ANABOLIC STEROIDS

Anabolic steroids have some androgenic activity but they cause less virilisation than androgens in women. They have protein-building property. Their use as body builders or tonics is unjustified; they are some times abused by some athletes. Anabolic steroids are used in the treatment of some aplastic anemia, and to reduce itching of chronic biliary obstruction.

NANDROLONE

Indications: osteoporosis in post menopausal women, aplastic anemia
Cautions: cardiac and renal impairment, hepatic impairment, hypertension, diabetes, epilepsy, migraine, monitor skeletal maturation in young patients, skeletal metastasis (risk of hypercalcemia)
Side-effects: acne, sodium retention with edema, virilisation, amenorrhoea, inhibition of spermetogenesis, premature epiphysial closure, abnormal liver function tests
Dose: for osteoporosis, 50 mg deep intramus-cular every 3 weeks; for palliative treatment in selected case of mammary carcinoma in women, 50mg by deep intramascular injection weekly

Proprietary Preparation
Decabolon *(Techno),* Inj., 50mg/ml, Tk. 112/Amp.; 25 mg/ml, Tk. 40/Amp.
Deca-Durabolin *(Nuvista)* Inj., 50mg/ml, Tk. 217.80/Amp
Durabolin *(Nuvista)*, Inj. 25 mg/ml Tk. 86.90/Amp
Hybolin *(Chemist),* Inj., Inj. 25 mg/ml Tk. 42.00/1 ml Amp.
Hydeca *(Chemist),* Inj., 50 mg/ml, Tk. 125.00/Amp.
Nandron *(Renata),* Inj., 25 mg/ml, Tk. 60/Amp.; 50 mg/ml, Tk. 160/Amp.

5.5 HYPOTHALAMIC AND PITUITARY HORMONES

5.5.1 HYPOTHALAMIC HORMONES

Gonadorelin if injected intravenously in normal subjects leads to a rapid rise in both Follicular Stimulating Hormone (FSH) and Leutinizing Hormone (LH). It can distinguish between hypothalamic and pituitary lesions. Gonadorelin is also used in treatment of infertility. Gonadorelin analogues are used in treatment of endometriosis and infertility and in breast and prostrate cancer. **Protirelin** if injected intravenously in normal subjects leads to a rapid rise in TSH; it fails to show such a response even in subclinical hyperthyroidism. So it is used in confirming difficult cases of hyperthyroidism. **Sermorelin**, an analogue of growth hormone releasing hormone is used in a diagnostic test for growth hormone secretion. **Somatostatin** is a polypeptide obtained from the hypothalamus or by synthesis. Somatostatin is usually given as the acetate in the treatment of gastrointes-tinal haemorrhage.

SOMATOSTATIN

Indications: upper gastrointestinal haemorrahage including variceal haemorrhage, insulin resistance, and the management of hormone-secreting tumours
Cautions: concomitant parenteral nutrition has been suggested because of the inhibitory effects of somatostatin on intestinal absorption; blood sugar should be monitored since somatostain may interfere with carbohydrate metabolism
Side-effects: abdominal discomfort, flushing, nausea, and bradycardia have been associated with too rapid administration
Dose: somatostatin is usually given as the acetate. 3.5 microgram/kg body-weight per hour has been given by intravenous infusion

Proprietary Preparations
Stilamin[(I)] *(Serono)* Inj., 3 mg, Tk. 5025.86/Vial

5.5.2 ANTERIOR PITUITARY HORMONES

5.5.2.1 GROWTH HORMONES

Growth hormone is required in the treatment of growth hormone deficiency. Only the growth hormone of human type

is effective. Human growth hormone (HGH) has been replaced by human sequence type **somatropin,** produced by using recombinant DNA technology.

SOMATROPIN

(Synthetic Human Growth Hormone)

Indications: *see under dose*
Cautions: diabetes mellitus, papill edema, relative deficiency of other pituitary hormones, history of malignant disease, slipped epiphysis of the hip, history of intracranial hypertension; avoid in pregnancy
Contraindications: evidence of tumour activity (start after completion of tumour treatment); renal trans-plantation ; for growth promotion in children with closed epiphysis
Side-effects: headache, visual disturbance (due to benign intracranial pressure fundoscopy); arthalgia, myalgia, peripheral edema due to fluid retention; antibody formation, transient reaction at injection site; leukaemia in children with growth hormone deficiency has also been reported
Dose: *by subcutaneous injection*, weekly dosage tailored for individual and given in 3, 6 or 7 divided doses (rotate injection sites); alternatively by intramuscular injection, weekly dosage given in 3 divided dose; in gonadal dysgenesis (Turner syndrome), 0.6–1.0 unit/kg weekly in divided doses subcutaneously; in children with growth hormone deficiency, 14–20 units/square meter body surface weekly in divided doses given subcutaneously or intramuscularly; in chronic renal failure in children, 30 units/square meter body surface weekly in divided doses given subcutaneously or intramuscularly; in adult with growth hormone deficiency, 0.125 to 0.25 units/kg weekly divided in daily doses subcutaneously or intramuscularly

Proprietary Preparation
Norditropin Simplex(ι) *(Novo Nordisk),* Inj. (Pre filled pen) 5mg/1.5ml.Tk.10901.22/pen.
Omnitrope(ι) *(Sandoz),* Inj.,3.3 mg/ml, Tk. 9,000.00/1 ml Cartridge

5.5.2.2 GONADOTROPINS

FSH and LH together (as in **human menopausal gonadotropin)** or FSH alone (as in **urofollitropin** or **follitropin**), are used in the treatment of infertility due to nonovulation or superovulation in assisted reproductive techniques (such as in vitro fertilization). **Gonadtrophins** are also used in treatment of oligospermia associated with hypopituitarism. **Chorionic gonadotropin** is also used in delayed puberty in male to stimulate endogenous testosterone production but has little advantage over testosterone.

HUMAN MENOPAUSAL GONADOTROPINS

Purified extract of human postmen-opausal urine containing FSH and LH; the relative *in vivo* activity is designated as a ratio; 1:1 ratio is known as menotropin.
Indications: *see notes above*
Cautions: ovarian cysts, adrenal or thyroid disorders, hyperprolactinmi or pituitary tumour
Side-effects: ovarian hyperstimulation, multiple pregnancy; local reactions
Dose: *by deep intramuscular injection* according to patient's response

Proprietary Preparation
Pergonal (ι) *(Serono)* Inj. 75 IU; Tk. 721.65/amp; 150IU Tk.1298.51/amp

UROFOLLITROPHIN

(Other name: Urofollitropin)

Extract of the urine of post menopausal women containing follicle-stimulating hormone
Indications: *see notes above*
Cautions & Side-effects: *see under human menopausal gonadotropins*
Dose: *by subcutaneous or intramuscular injection* according to patient's response

Proprietary Preparation
FSH50 *(Popular),*Inj.,50IU/vial,Tk.1375.00/vial

FOLLITROPIN ALFA and BETA

(Recombinant human follicular stimulating hormone)

Indications: *see notes above*
Cautions; *Side-effects: see under human menopausal gonadotropins*
Dose: *by* subcutaneous injection according to patient's response

Proprietary Preparations
Gonal F (I) *(Serono),* Inj. (P.Fsyringe).75IU. Tk.1889.13/syringe
Puregon (I) *(Organon),* Inj. 50 IU, Tk.2600.00/amp 100 IU; Tk. 5100.00/amp.

CHORIONIC GONADOTROPHIN

(Human Chorionic Gonadotropin; HCG)

A preparation of a glycoprotein fraction secreted by the placenta and obtained from the urine of pregnant women, having the action of pituitary luteinising hormone
Indications: *see notes above*
Cautions: *see notes above*; cardiac and renal impairment, asthma, epilepsy, migraine
Side-effects: edema, headache, tiredness, mood changes, gynaeco-mastia, local reactions; sexual precocity with high doses; ovarian hyper stimulation syndrome has been reported
Dose: *by subcutaneous or intramuscularly injection* according to patient's response

Proprietary Preparations
HCG5000 *(Popular)*, Inj., 5000IU, Tk.1300/vial
Ovidril(I) *(Serono),* Inj., 250 microgram, Tk. 4695.65/ Vial
Pregnyl(I)*(Organon),*Inj.5000IU.Tk.2350/amp

5.5.2.3 CORTICOTROPINS

Tetracosactrin an analogue of corticotropins (ACTH) is used to test adrenocortical function. Failure of the plasma cortisol to rise after intramuscular administration indicates adrenal insufficiency. Corticotrophins were formerly used as alternatives to corticosteroids in conditions such as Crohn's disease or rheumatoid arthritis.

5.5.3 POSTERIOR PITUITARY HORMONES AND ANTAGONISTS

Vasopressin (Antidiuretic hormones, ADH) is used in treatment of cranial diabetes insipidus, as is its analogue **desmopressin**. The synthetic form of vasopressin is known as **argipressin.** Dosage is tailored according to response; slight diuresis is maintained to avoid water intoxication. Diabetes insipidus after trauma or pituitary surgery may be transient; so a short period of treatment may be enough. **Desmopressin** has a longer duration of action than vesopressin; unlike vesopressin it has no vasoconstricting effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in uncon-scious patients. **Desmopressin** is also used in differential diagnosis of diabetes insipidus. Following a dose of 2 micrograms intramuscularly or 20 micrograms intranasally, restoration of urine concentration capacity after a water deprivation confirms a diagnosis of cranial diabetes insipidus; a failure to produce such a response indicates nephrogenic diabetes insipidus. In nephrogenic and partial cranial (pituitary) diabetes insipidus, benefit may be gained from the paradoxical antidiuretic effect of thiazide (e.g. **chlorthalidone** 100 mg twice daily, reduced to 50 mg daily for maintenance). **Chlorpropamide** is also used in partial cranial diabetes insipidus; it acts by increasing renal tubular sensitivity to vasopressin (e.g. **chlorpropamide** 250 mg once daily for adult; 125–200 mg once daily in children); care must be taken so that hypoglycemia does not occur. **Carbamazepine** is also used with limited success (dose: 200 mg daily); its mode of action is similar to that of chlorpropamide.
Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and for the control of nocturnal enuresis. Vasopressin infusion is used to control variceal bleeding in portal hypertension.

Terlipressin has effects milder than vasopressin and is used to control bleeding from oesophageal varices.
Oxytocin, another posterior pituitary hormone is used in obstetrics *(see section 6.1.1).*

ANTIDIURETIC HORMONE ANTAGONISTS

Demeclocycline may be used in the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormones. It is thought to act by directly blocking the renal tubular effect of anti-diuretic hormones. Initial dose: 0.9-1.2 g daily in divided dose; maintenance with 600-900 mg daily.

5.6 DRUGS AFFECTING BONE METABOLISM

5.6.1 BISPHOSPHONATES
5.6.2 CALCITONIN

Osteoporosis is a quantitative reduction of bone with increased fragility. This is common sequelae of aging process and is more marked in postmenopausal woman. Risk factors for osteoporosis include corticosteroid therapy, lack of physical activity, low body weight, smoking, alcoholism, and calcium and vitamin D deficiency. Other causes include hyperthyroidism, hyperparathyroidism, hypogonadism and Cushing's disease.
Early treatment of osteoporosis is useful to prevent its complications. For any established complication (e.g. development of a low trauma fracture), therapy is strongly indicated. The therapeutic options for treatment and prophylaxis are the same:

Those at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and anydeficiency should be corrected by increasing dietary intake or taking supplements.

Post-menopausal osteoporosis. Bisphosphonates (alendronic acid and risedronate, section 5.6.1) are effective for preventing postmenopausal Osteoporosis, if phosphonates are unsuitable Calcitriol (section16.2.3.4) or strontium ranelate may be considered. Hormone replacement therapy (HRT section 5.4.1.1) is an option where other therapies are contraindicated, cannot be tolerated, or if there is a lack of response. Calcitonin is no longer recommended for
the treatment of postmenopausal osteoporosis as the benefits are outweighed by the risk of malignancy associated with long-term use. Parathyroid hormone, and teriparatide have been introduced for the treatment of postmenopausal osteoporosis.

Corticosteroid induced osteoporosis. The dose of corticosteroid should be as low as possible and the course as short as possible to reduce the chance of osteoporosis. With a dose of prednisolone 7.5mg/day or more for 3 months or longer, the patient should be assessed for osteoporosis. During corticosteroid therapy, age of 65 years and above constitute a high-risk group. During prolonged therapy the maximum bone loss occurs during the first 6-12 months.

5.6.1 BISPHOSPHONATES

The bisphosphonates (**alendronic acid, disodium etidronate, disodium pamidronate, ibandronic acid, sodium clodronate**) become absorbed on to bone crystals (hydroxyapetite) conferring resistance to hydrolysis and prolonging of half-life in the skeleton. Also when the complex is phagocytosed by an osteoclast that cell is inhibited and can not reabsorb more bone.
Bisphosphonates are used in the treatment of Paget's disease, osteoporosis in postmenopausal women and hypercalcaemia due to cancer. They may be given orally or intravenously. Bioavailability of oral bisphosphonates is very poor and constitutes only 10 percent and the rest is eliminated unchanged by the kidney. Fall in serum

calcium begins in 1-2 days, reaches a nadir in 5-6 days and lasts for 20-30 days.

ALENDRONIC ACID

Indications: treatment of osteoporosis in postmenopausal women
Side-effects: pyrexia, diarrhoea, oesophageal reactions, abdominal pain and distension, headache, nausea, vomiting, increase of bone pain. Long term use of high dose may cause fracture of bone and esophageal irritation
Cautions: gastritis, dysphagia, vitamin D deficiency, renal impairment
Contraindications: strictures of oesophagus, achalasia, hypocalcaemia and breast-feeding
Interactions: *see Appendix-2*
Dose: treatment of post-menopausal osteoporosis 10 mg daily or 70mg once weekly at least 30 minutes before breakfast
COUNSELLING: Swallow the tablet whole with a full glass of water on an empty stomach at least 30 minutes before breakfast; stand or sit upright for at least 30 minutes and do not lie down until after eating breakfast. Do not take the tablets at bedtime or before rising

Proprietary Preparations
Ostel *(Square),* Tab., 70 mg,Tk. 25.10/Tab.;10 mg, Tk. 5.01/Tab.
Alendronic acid + Colecalciferol
Ostel-D 70/2800 *(Square),*Tab. ,70 mg + 2800 IU, Tk. 30.11/Tab. ;Tab. , 10 mg + 400 IU, Tk. 6.02/Tab
Bonemass D *(Incepta)*, Tab.,70 mg + 2800 IU Tk.30.00/Tab

IBANDRONIC ACID

Indications: hypercalcaemia induced by metastatic bone diseases
Cautions: hepatic impairment; monitor renal function and serum calcium, phosphate and magnesium; cardiac disease (avoid volume over load); *not recommended for use in children*
Contraindications: moderate to severe renal impairment, pregnancy, breast-feeding
Side-effects: hypocalcaemia, hypophos-phatemia, flu-like symptoms including fever, chills, muscle and bone pain reported; rarely hypersensitivity reactions; bronchospasm and angioe-dema reported
Dose: *by mouth,* 150mg once a month in empty stomach at least 30 minutes before breakfast (Counselling as for Alandronic Acid)
by intravenous infusion, according to serum calcium concentration, 2-4 mg in single infusion; CHILD not recommended

Proprietary Preparations
Bondronat (I) *(Roche),* Inj., 6 mg/6 ml, Tk. 25,990.00/6 ml Vial
Bondrova *(Healthcare),* Tab., 150 mg, Tk. 1,960.00/Tab.
Bone-Guard *(Incepta),* Tab. , 150 mg, Tk. 510.00/Tab.
Bonfix *(Opsonin),* Tab., 150 mg, Tk. 676.69/Tab.
Bonova *(Radiant),* Tab. , 150 mg, Tk.2,500.00/Tab.
Bonviva(I) *(Vetter),* Inj., 3 mg/3 ml, 1, Tk. 7,196.96/3 ml Vial
Ibandron *(Aristo),* Tab. , 150mg, Tk. 1,200.00/Tab.
Idrofos*(Sun),* Tab. , 150 mg, Tk. 1500.00/Tab.
Lasibon (I)(*Pharmathen),*2mg/2ml Tk. 158.90/62ml Vial
Calcium Orotate 400 mg and Ibandronic Acid 150 mg (KIT)
Calorate Kit *(Beximco),* Kit, 400 mg Tab. & 150 mg Tab., 1's, Tk. 990.00/Kit

RISEDRONATE SODIUM

Indications: *see under dose*
Cautions: oesophageal abnormalities and other factors which delay transit or emptying (e.g. stricture or achalasia-*see under side-effects*); renal impairment (manufacturer advises avoid if creatinine clearance is less than 30mL/minute); correct hypocalcaemia before starting, correct other disturbances of bone and mineral metabolism (e.g. vitamin-D deficiency) at onset of treatment
Interactions: *see Appendix- 2*
Contraindications: hypocalcaemia *(see Cautions above),* pregnancy and breast-feeding

Side-effects: gastro-intestinal effects (including dyspepsia, nausea, diarrhoea, constipation, oesophageal stricture, and duodenitis); dizziness, headache; influenza-like symptoms, musculos-keletal pain, rarely glossitis, edema, weight loss, apnoea, bronchitis, sinusitis, rash, nocturia, ambylopia, corneal lesion, dry eye, tinnitus, iritis
Dose: Paget's disease of bone, 30mg daily for 2 months; may be repeated if necessary after at least 2 months
treatment of postmenopausal osteoporosis to reduce risk of vertabral or hip fractures, 5 mg daily or 35 mg once weekly
prevention of osteoporosis (including corticosteroid induced osteoporosis) in postmenopausal women, 5mg daily
COUNSELLING. swallow tablets whole with full glass of water; on rising, in empty stomach at least 30 minutes before first food or drink of the day or, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after risedronate (particularly avoid calcium-containing products e.g. milk, also avoid iron and mineral supplements and antacids); stand or sit upright for at least 30 minutes; do not take tablets at bedtime or before rising

Proprietary Preparations
Risedon*(Square),* Tab. 150 mg, Tk.120/Tab.
Risonet*(Opsonin),* Tab.150 mg, Tk. 120.00/Tab.; 35 mg, Tk. 50.00/Tab.
Salost*(Unimed),* Tab. 150 mg, Tk. 200/Tab.; 35 mg, Tk. 50/Tab.;5 mg, Tk. 8/Tab.
Sedron *(General),* Tab. 35 mg, Tk. 35.14/Tab.; 5 mg, Tk. 8.03/Tab

ZOLEDRONIC ACID

Indications: *see under dose*
Cautions: monitor serum electrolytes, calcium, phosphate and magnesium, assess renal function before each dose, renal impairment severe hepatic impairment; cardiac disease (avoid fluid overload)
Interactions: *see Appendix-2*
Contraindications: pregnancy, breast-feeding
Side-effects: hypophosphataemia, anemia, influenza-like symptoms including bone pain, fever and rigors gastro-intestinal effects including nausea, vomiting, and anorexia, headache, conjunctivitis renal impair-ment (rarely acute renal failure); rarely diarrhoea, constipation, taste disturba-nce, dry mouth, stomatitis, chest pain, dyspnoea, cough, dizziness, paraesth-esia, tremor, anxiety, sleep disturbance, blurred vision, weight gain, pruritus, rash, sweating, haematuria, proteinuria, hypersensitivity reactions (including angiedema) peripheral edema, thrombocytopenia, leucopenia, hypomagnesa-emia, also injection site reactions; very rarely bradycardia, confusion, hyperkal-aemia, hypokaleamia, hypernatraemia, pancytopenia
Dose: for post-menopausal osteoporosis and osteoporosis in men by intravenous infusion, 5mg as a single dose over at least 15 minutes, once a year
reduction of bone damage in advanced malignancies involving bone (with calcium and vitamin D supplement), by intravenous infusion, 4 mg every 3-4 weeks
Hypercalcaemia of malignancy, by intravenous infusion 4mg as a single dose.

Proprietary Preparation
Aclasta[I] *(Novartis),* Inj.,(IV Infusion), 0.05%, Tk. 32500.00/Vial
Xoleron *(Beacon),* Inj., 4 mg/5 ml, Tk. 5,000.00/Vial
Zoledron *(Opsonin),* Inj.,(IV Infusion), 0.05%,, Tk. 4,473.68/100 ml
Zolenic *(Incepta),* Inj.,(IV Infusion), 0.05%, Tk. 5,947.00/10;Inj., 4 mg/5 ml, Tk. 5,000.00/Vial
Zometa[I] *(Novartis),* Inj.,(IV Infusion), 4 mg/5 ml, Tk. 30000.00/Vial

5.6.2 CALCITONIN

Calcitonin is a peptide hormone produced by the C-cell of thyroid. It acts on bone to inhibit osteoclasts to reduce the rate of bone turnover, and on kidney to reduce the reabsorption of calcium

and phosphate. It is used to lower the plasma calcium concentration in some patients with hypercalcaemia, especially associated with malignant disease. Effect on serum calcium is observed within 4-6 hours and last for 6-10 hours only. Prolonged used of porcine calcitonin can lead to production of neutralizing antibodies. **Salcatonin,** the partially synthesized calcitonin derived from salmon is less immunogenic and is more suitable for long-term therapy.

Indications: paget's disease; hypercalcaemia; *see notes above and also under dose.*

Cautions: history of allergy, heart failure, breast feeding, pregnancy

Side-effects: Inflammatory reactions at injection site, gastrointestinal upset, allergic reactions, flushing, tingling sensation in hands

Dose: in Paget's disease of bone, *by subcutaneous or intramuscular injection,* dose range 50 units 3 times weekly to 100 units daily, in single or divided doses

In hypercalcaemia, *by subcutaneous or intramuscular injection,* initially 4 units/kg daily adjusted according to clinical and biochemical response

Proprietary Preparations

Miacalcic(I) *(Novartis),* Injection, 100 IU/ml, Tk. 591.00/Vial

Miacalcic(I) *(Delpharm),* Nasal Spray, 200 IU/ml, Tk. 2958.00/ml