how toxic it is and whether it is eliminated entirely by renal excretion or is partly metabolized to inactive metabolites.

In general, all patients with renal impairment are given a loading dose which is the same as the usual dose for a patient with normal renal function. Maintenance doses are adjusted to the clinical situation. The maintenance dose of a drug can be reduced either by reducing the individual dose leaving the normal interval between doses unchanged or by increasing the interval between doses without changing the dose. The interval extension method may provide the benefits of convenience and decreased cost, while the dose reduction method provides more constant plasma concentration.

Renal impairment is usually divided into three grades:

1. **Mild** : GFR 20–50 ml/minute or approximate serum creatinine 150–300 micromol/litre
2. **Moderate** : GFR 10–20 ml/minute or serum creatinine 300–700 micromol/litre
3. **Severe** : GFR <10 ml/minute or serum creatinine >700 micromol/litre

When using the dosage guidelines the following must be considered:

- Drug prescribing should be kept to a minimum.
- Nephrotoxic drugs should, if possible, be avoided in all patients with renal disease because the nephrotoxicity is more likely to be serious.
- It is advisable to determine renal function not only before but also during the period of treatment and adjust the maintenance dose as necessary.
- Renal function (GFR, creatinine clearance) declines with age so that by the age of 80 it is half that in healthy young subjects. When prescribing for the elderly, assume at least a mild degree of renal impairment.
- Uraemic patients should be observed carefully for unexpected drug toxicity. In these patients the complexity of clinical status as well as other variables for example altered absorption, protein binding or metabolism, or liver function, and other drug therapy precludes use of fixed drug dosage and an individualized approach is required.

In the following table drugs are listed in alphabetical order. The table includes only drugs for which specific information is available. Many drugs adjustment is available; it is therefore important to also refer to the individual drug entries. The recommendations are given for various levels of renal function as estimated by the glomerular filtration rate (GFR), usually measured by the creatinine clearance (best calculated from a 24-hour urine collection). The serum-creatinine concentration is sometimes used instead as a measure of renal function but it is only a rough guide even when corrected for age, sex and weight by special nomograms.

Drugs to be avoided or used with caution in renal impairment:

Table 1.4 : Drugs and Renal impairment

Drug	Grade	Comment
Abacavir	Severe	Avoid
Acetazolamide	Mild	Avoid; metabolic acidosis
Aciclovir	Mild	Reduce intravenous dose Moderate to severe: Reduce dose

Drug	Grade	Comment
Allopurinol	Moderate	100–200 mg daily; increased toxicity; rashes Severe 100 mg on alternate days (maximum 100 mg daily)
Aluminium hydroxide	Severe	Aluminium is absorbed and may accumulate NOTE. Absorption of aluminium from aluminium salts is increased by citrates which are contained in many effervescent preparations (such as effervescent analgesics)
Amiloride	Mild	Monitor plasma potassium; high risk of hyperkalaemia in renal impairment; excreted by kidney unchanged
	Moderate	Avoid
Amoxicillin	Mild to moderate	Risk of crystalluria with high doses
	Severe	Reduce dose; rashes more common and risk of crystalluria
Amphotericin B	Mild	Use only if no alternative; nephrotoxicity may be reduced with use of lipid formulations
Ampicillin	Severe	Reduce dose; rashes more common
Artemether + lumefantrine	Severe	Caution; monitor ECG and plasma potassium
Aspirin	Severe	Avoid; sodium and water retention; deterioration in renal function; increased risk of gastrointestinal bleeding
Atenolol	Mild to moderate	Reduce dose to max. 50 mg daily if creatinine clearance 15–35 ml/minute
	Severe	May reduce renal blood flow and adversely affect renal function; reduce dose to max. 25 mg daily if creatinine clearance less than 15 ml/minute
Azathioprine	Severe	Reduce dose
Benzathine benzylpenicillin	Severe	Neurotoxicity—high doses may cause convulsions
Benzylpenicillin	Severe	Maximum 6 g daily; neuro-toxicity—high doses may cause convulsions
Bleomycin	Moderate	Reduce dose
Carbamazepine		Manufacturer advises caution
Cefixime	Moderate	Reduce dose
Ceftazidime	Mild	Reduce dose
Ceftriaxone	Severe	Maximum 2 g daily; also monitor plasma concentration if both severe renal impairment and hepatic impairment
Chlorambucil	Moderate	Use with caution and monitor response; increased risk of myelo-suppression
Chloramphenicol	Severe	Avoid unless no alternative; dose-related depression of haematopoiesis
Chloroquine	Mild to moderate	Reduce dose in rheumatic disease
	Severe	Reduce dose for malaria prophylaxis; avoid in rheumatic disease

Drug	Grade	Comment
Chlorpheni-ramine	Severe	Dose reduction may be required
Chlorpromazine	Severe	Start with small doses; increased cerebral sensitivity
Ciclosporin	Mild	Monitor kidney function—dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction (exclude rejection if kidney transplant)
Ciprofloxacin	Moderate	Use half normal dose
Cisplatin	Mild	Avoid if possible; nephrotoxic and neurotoxic
Cloxacillin	Severe	Reduce dose
Codeine	Moderate to severe	Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity
Cyclophospha-mide	Mild	Reduce dose
Dacarbazine	Mild to moderate	Dose reduction may be required
	Severe	Avoid
Daunorubicin	Mild to moderate	Reduce dose
Deferoxamine	Severe	Metal complexes excreted by kidneys (in severe renal impairment dialysis increases rate of elimination)
Diazepam	Severe	Start with small doses; increased cerebral sensitivity
Didanosine	Mild	Reduce dose; consult manufacturer's literature
Diethyl-carbamazine	Moderate to severe	Reduce dose; plasma half life prolonged and urinary excretion considerably reduced
Digoxin	Mild	Reduce dose; toxicity increased by electrolyte disturbances
Doxycycline	Mild	Use with caution; avoid excessive doses
Efavirenz	Severe	No information available—caution advised
Enalapril	Mild	Use with caution and monitor response; initial dose 2.5 mg once daily if creatinine clearance less than 30 ml/minute. Hyperkalaemia and other adverse effects more common
Ephedrine	Severe	Avoid; increased CNS toxicity
Ergometrine	Severe	Manufacturer advises avoid
Erythromycin	Severe	Maximum 1.5 g daily (ototoxicity)
Ethambutol	Mild	Reduce dose; if creatinine clearance less than 30 ml/minute monitor plasma ethambutol concentration; optic nerve damage
Etoposide	Mild	Consider dose reduction
Fluconazole	Mild to moderate	Usual initial dose then halve subsequent doses
Flucytosine	Mild	Reduce dose if creatinine clearance<40 ml/min and monitor plasma-flucytosine concentration; consult manufacturer's literature
Fluphenazine	Severe	Start with small doses; increased cerebral sensitivity

Drug	Grade	Comment
Furosemide	Moderate	May need high doses; deafness may follow rapid i/v injection
Gentamicin	Mild	Reduce dose; monitor plasma concentrations
Glibenclamide	Severe	Avoid
Haloperidol	Severe	Start with small doses; increased cerebral sensitivity
Heparin	Severe	Risk of bleeding increased
Hydralazine	Mild	Reduce dose if creatinine clearance less than 30 ml/minute
Hydrochloro-thiazide	Moderate	Avoid; ineffective
Ibuprofen	Mild	Use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly leading to renal failure
	Moderate to severe	Avoid
Imipenem + cilastatin	Mild	Reduce dose
Insulin	Severe	May need dose reduction; insulin requirements fall; compensatory response to hypoglycaemia is impaired
Iohexol	Moderate to severe	Increased risk of nephrotoxicity; avoid dehydration
Iopanoic acid	Mild to moderate	Maximum 3 g
	Severe	Avoid
Isoniazid	Severe	Maximum 200 mg daily; peripheral neuropathy
Lamivudine	Mild	Reduce dose; consult manufacturer's literature
Lidocaine	Severe	Caution
Lithium	Mild	Avoid if possible or reduce dose and monitor plasma concentration carefully
	Moderate	Avoid
Lopinavir + ritonavir	Severe	Avoid oral solution due to propylene glycol content; use tablet/capsules with caution in severe impairment
Magnesium hydroxide	Moderate	Avoid or reduce dose; increased risk of toxicity
Magnesium sulfate	Moderate	Avoid or reduce dose; increased risk of toxicity
Mannitol	Severe	Avoid unless test dose produces diuretic response
Meglumine antimoniate	Moderate	see pentavalent antimony compounds
Meglumine iotroxate	Moderate to severe	Increased risk of nephrotoxicity; avoid dehydration
Mercaptopurine	Moderate	Reduce dose
Metformin	Mild	Avoid; increased risk of lactic acidosis
Methadone	Moderate to severe	Increased and prolonged effect; increased cerebral sensitivity

Drug	Grade	Comment
Methotrexate	Mild	Reduce dose; accumulates; nephrotoxic
	Moderate	Avoid
Methyldopa	Moderate	Start with small dose; increased sensitivity to hypotensive and sedative effect
Metoclopramide	Severe	Avoid or use small dose; increased risk of extrapyramidal reactions
Morphine	Moderate to severe	Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity
Neostigmine	Moderate	May need dose reduction
Nitrofurantoin	Mild	Avoid; peripheral neuropathy; ineffective because of inadequate urine concentrations
Penicillamine	Mild	Reduce dose and monitor renal function
	Moderate to severe	Avoid
Pentamidine isetionate	Mild	Reduce dose; consult manufacturer's literature
Pentavalent antimony compounds	Moderate	Increased adverse effects
	Severe	Avoid
Phenobarbital	Severe	Avoid large doses
Povidone iodine	Severe	Avoid regular application to inflamed or broken mucosa
Potassium chloride	Moderate	Avoid routine use; high risk of hyperkalaemia
Procainamide	Mild	Avoid or reduce dose
Procaine penicillin	Severe	Neurotoxicity—high doses may cause convulsions
Procarbazine	Severe	Avoid
Proguanil	Mild	100 mg once daily
	Moderate	50 mg on alternate days
	Severe	50 mg once weekly; increased risk of haematological toxicity
Propranolol	Severe	Start with small dose; higher plasma concentrations after oral administration; may reduce renal blood flow and adversely affect renal function
Propylthiouracil	Mild to moderate	Use three-quarters normal dose
	Severe	Use half normal dose
Pyridostigmine	Moderate	Reduce dose; excreted by kidney
Quinine	Severe	Reduce parenteral maintenance dose for malaria treatment to 5-7 mg/kg
Ranitidine	Severe	Use half normal dose; occasional risk of confusion
Ritonavir	Severe	see lopinavir with ritonavir
Saquinavir	Severe	Dose adjustment possibly required
Sodium chloride	Severe	Avoid
Sodium bicarbonate	Severe	Avoid; specialized role in some forms of renal disease

Drug	Grade	Comment
Sodium nitroprusside	Moderate	Avoid prolonged use
Spironolactone	Mild	Monitor plasma K+; high risk of hyperkalaemia in renal impairment
	Moderate	Avoid
Stavudine	Mild	20 mg twice daily (15 mg if body weight less than 60 kg)
	Moderate to severe	20 mg once daily (15 mg if body weight less than 60 kg)
Streptomycin	Mild	Reduce dose; monitor plasma concentrations
Sulfadiazine	Severe	Avoid; high risk of crystalluria
Sulfamethoxazole + trimethoprim	Mild	Use half normal dose if creatinine clearance 15–30 ml/minute; avoid if creatinine clearance less than 15 ml/minute and if plasma-sulfamethoxazole concentration cannot be monitored
Sulfasalazine	Moderate	Risk of toxicity including crystalluria—ensure high fluid intake
	Severe	Avoid
Trimethoprim	Mild	Use half normal dose after 3 days if creatinine clearance 15–30 ml/minute
	Moderate to severe	Use half normal dose if creatinine clearance less than 15 ml/minute; avoid if creatinine clearance less than 10 ml/minute (unless plasma-trimethoprim concentration monitored)
Valproic acid	Mild to moderate	Reduce dose
	Severe	Alter dosage according to free serum valproic acid concentration
Vancomycin	Mild	Reduce dose—monitor plasma-vancomycin concentration and renal function regularly
Warfarin	Severe	Avoid
Zidovudine	Severe	Reduce dose; manufacturer advises oral dose of 300–400 mg daily in divided doses or intravenous dose of 1 mg/kg 3–4 times daily

13. Prescribing in hepatic impairment

Liver disease may alter the response to drugs. However, the hepatic reserve appears to be large and liver disease has to be severe before important changes in drug metabolism take place. The ability to eliminate a specific drug may or may not correlate with the liver's synthetic capacity for substances such as albumin or clotting factors, which tends to decrease as hepatic function declines. Unlike renal disease, where estimates of renal function based on creatinine clearance correlate with parameters of drug elimination such as clearance and half-life, routine liver function tests do not reflect actual liver function but are rather markers of liver cellular damage.

The altered response to drugs in liver disease can include all or some of the following changes:

- Impaired intrinsic hepatic eliminating (metabolizing) capacity due to lack of or impaired function of hepatocytes.