Abacavir

Clinical use

Nucleoside reverse transcriptase inhibitor:

- Used for HIV infection in combination with other antiretroviral drugs

Dose in normal renal function

600 mg daily in 1 or 2 divided doses

Pharmacokinetics

Molecular weight (daltons)	286.3 (670.7 as sulphate)
% Protein binding	49
% Excreted unchanged in urine	2
Volume of distribution (L/kg)	0.8
Half-life — normal/ESRF (hrs)	1.5 / Unchanged

Metabolism

Abacavir is primarily metabolised by the liver with approximately 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. The metabolites are excreted in the urine.

Dose in renal impairment GFR (mL/min)

20–50	Dose as in normal renal function.
10–20	Dose as in normal renal function.
<10	Dose as in normal renal function.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Unknown dialysability. Dose as in normal renal function.
HD	Unlikely to be dialysed. Dose as in normal renal function.
HDF/High flux	Not dialysed. Dose as in normal renal function.
CAV/VVHD	Unknown dialysability. Dose as in normal renal function.

Important drug interactions

Potentially hazardous interactions with other drugs

- Antivirals: possibly reduces effects of ribavirin; concentration reduced by tipranavir.
- Orlistat: absorption possibly reduced by orlistat.

Administration

Reconstitution

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Route

Oral

Rate of administration

—

A

Abatacept

Clinical use

Treatment of moderate to severe rheumatoid arthritis and psoriatic arthritis in people who have not responded adequately to other treatment

Dose in normal renal function

IV:

- Loading doses: <60 kg: 500 mg, 60–100 kg: 750 mg, >100 kg: 1000 mg repeated 2 and 4 weeks after initial infusion
- Then 125 mg weekly (SC)

Psoriatic arthritis:

- 125 mg weekly (SC)

Pharmacokinetics

Molecular weight (daltons)	92 000
% Protein binding	No data
% Excreted unchanged in urine	No data
Volume of distribution (L/kg)	0.07
Half-life — normal/ESRF (hrs)	13.1 days / –

Metabolism

Abatacept is cleared via Fc-mediated phagocytosis.

Dose in renal impairment GFR (mL/min)

20–50	Dose as in normal renal function.
10–20	Dose as in normal renal function. Use with caution.
<10	Dose as in normal renal function. Use with caution.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Unlikely to be dialysed. Dose as in GFR<10 mL/min.
HD	Unlikely to be dialysed. Dose as in GFR<10 mL/min.
HDF/High flux	Unlikely to be dialysed. Dose as in GFR<10 mL/min.
CAV/VVHD	Unlikely to be dialysed. Dose as in GFR=10–20 mL/min.

Important drug interactions

Potentially hazardous interactions with other drugs

- Avoid with certolizumab, etanercept, golimumab and infliximab.
- Vaccines: avoid concomitant use with live vaccines.

Administration

Reconstitution

With 10 mL of water for injection per vial

Route

IV infusion, SC

Rate of administration

Over 30 minutes

Comments

- DO NOT SHAKE when reconstituting.
- Add dose to 100 mL of sodium chloride 0.9%.

Other information

- Stable for 24 hours at 2–8°C if made under aseptic conditions.
- Administer with an infusion set with a low protein binding filter (pore size 0.2–1.2 μm).
- Manufacturer does not have any information on its use in renal impairment. Main side effects are infections and malignancies, to which renal patients may be at increased risk, therefore use with caution.

Abciximab

Clinical use

Antiplatelet agent:

- Prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention
- Short-term prevention of myocardial infarction in patients with unstable angina not responding to treatment or awaiting percutaneous coronary intervention.

Dose in normal renal function

IV bolus: 250 mcg/kg then by infusion at 0.125 mcg/kg/minute for 12 hours after intervention (maximum 10 mcg/minute).

Pharmacokinetics

Molecular weight (daltons)	47 455.4
% Protein binding	Binds to platelets.
% Excreted unchanged in urine	Minimal (catabolised like other proteins)
Volume of distribution (L/kg)	0.118[1]
Half-life — normal/ESRF (hrs)	<10 minutes / Unchanged

Metabolism

Following IV administration, abciximab rapidly binds to the platelet GPIIb/IIIa receptors, and remains in the circulation for 15 days or more in a platelet-bound state. Metabolism is via proteolytic cleavage

Dose in renal impairment GFR (mL/min)

20–50	Dose as in normal renal function.
10–20	Dose as in normal renal function.
<10	Dose as in normal renal function. Use with caution. See 'Other information'.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Unlikely to be dialysed. Dose as in GFR<10 mL/min.
HD	Unlikely to be dialysed. Dose as in GFR<10 mL/min.
HDF/High flux	Unlikely to be dialysed. Dose as in GFR<10 mL/min.
CAV/VVHD	Unlikely to be dialysed. Dose as in normal renal function.

Important drug interactions

Potentially hazardous interactions with other drugs

- Heparin, anticoagulants, antiplatelets and thrombolytics: increased risk of bleeding.

Administration

Reconstitution

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Route

IV bolus, IV infusion

Rate of administration

Bolus: 1 minute; Infusion: 0.125 mcg/kg/minute (maximum 10 mcg/minute)

Comments

Dilute in sodium chloride 0.9% or glucose 5%. Give via a non-pyrogenic low-protein-binding 0.2, 0.22 or 5 micron filter.

Other information

- Increased risk of bleeding in CKD 5, benefits of abciximab treatment may be reduced.
- In the UK the licence says use with caution in severe renal disease due to increased risk of bleeding and benefits may be reduced. It also advises to avoid in haemodialysis patients due to increased risk of bleeding (as on heparin for dialysis) but it is used in normal doses in the USA.
- Antibodies to abciximab develop 2–4 weeks post dose in 5.8% of patients so monitor for hypersensitivity reactions if re-administered.
- Abciximab remains in the body for at least 15 days, bound to platelets.
- Once infusion is stopped, the concentration of abciximab falls rapidly for 6 hours then decreases at a slower rate.

Reference:

1. Mager DE, Mascelli MA, Kleiman NS, *et al.* Simultaneous modelling of abciximab plasma concentrations and ex vivo pharmacodynamics in patients undergoing coronary angioplasty. *J Pharmacol Exp Ther*. 2003; **307**(3): 969–76.

A

Abiraterone acetate

Clinical use

Hormone antagonist:
- Treatment of metastatic prostate cancer

Dose in normal renal function

1000 mg daily

Pharmacokinetics

Molecular weight (daltons)	391.6
% Protein binding	99.8
% Excreted unchanged in urine	5
Volume of distribution (L/kg)	5630 Litres
Half-life — normal/ESRF (hrs)	15 / Unchanged

Metabolism

Abiraterone acetate is hydrolysed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation mainly in the liver to form inactive metabolites. About 88% of a dose is excreted in the faeces, of which about 55% is unchanged abiraterone acetate and about 22% is abiraterone; about 5% of a dose is excreted in the urine.

Dose in renal impairment GFR (mL/min)

20–50	Dose as in normal renal function.
10–20	Dose as in normal renal function.
<10	Dose as in normal renal function.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Unlikely to be dialysed. Dose as in normal renal function.
HD	Not dialysed. Dose as in normal renal function.
HDF/High flux	Not dialysed. Dose as in normal renal function.
CAV/VVHD	Unlikely to be dialysed. Dose as in normal renal function.

Important drug interactions

Potentially hazardous interactions with other drugs
- Antibacterials: concentration possibly reduced by rifabutin and rifampicin – avoid.
- Antidepressants: concentration possibly reduced by St John's wort – avoid.
- Antiepileptics: concentration possibly reduced by carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone – avoid.

Administration

Reconstitution
—

Route
Oral

Rate of administration
—

Comments
Should be taken on an empty stomach.

Other information

- The manufacturer suggests using normal doses in renal patients although no formal studies have been done so use with caution.

Acamprosate calcium

Clinical use

Maintenance of abstinence in alcohol dependence

Dose in normal renal function

- >60 kg: 666 mg 3 times a day
- <60 kg: 666 mg at breakfast, 333 mg at midday and 333 mg at night

Pharmacokinetics

Molecular weight (daltons)	400.5
% Protein binding	0
% Excreted unchanged in urine	Majority
Volume of distribution (L/kg)	Approximately 1
Half-life — normal/ESRF (hrs)	33 / 85.8

Metabolism

Acamprosate is excreted in the urine and is not metabolised significantly.

Dose in renal impairment GFR (mL/min)

30–50	333 mg 3 times daily.
10–30	333 mg twice daily. See 'Other information'.
<10	333 mg once daily. See 'Other information'.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Dialysed. Dose as in GFR<10 mL/min.
HD	Dialysed. Dose as in GFR<10 mL/min.
HDF/High flux	Dialysed. Dose as in GFR<10 mL/min.
CAV/VVHD	Dialysed. Dose as in GFR=10–30 mL/min.

Important drug interactions

Potentially hazardous interactions with other drugs

- None known

Administration

Reconstitution

—

Route

Oral

Rate of administration

—

Other information

- Recommended treatment period is a year.
- In USA manufacturer advises to avoid if GFR<30 mL/min, in the UK it is contraindicated if creatinine >120 micromol/L.
- Doses estimated from evaluation of pharmacokinetic data, use with caution in moderate to severe renal impairment.
- After a single dose of 666 mg in patients with severe renal impairment, the average maximum concentration was 4 times that in healthy individuals.
- Bioavailability is reduced if administered with food.

A

Acarbose

Clinical use

Antidiabetic agent

Dose in normal renal function

50–200 mg 3 times a day

Pharmacokinetics

Molecular weight (daltons)	645.6
% Protein binding	15
% Excreted unchanged in urine	1.7 (35% including inactive metabolites)
Volume of distribution (L/kg)	0.32
Half-life — normal/ESRF (hrs)	3–9 / Increased

Metabolism

Oral bioavailability is 1–2%. After oral administration of the ^{14}C-labelled substance, on average, 35% of the total radioactivity was excreted by the kidneys within 96 hours. The proportion of drug excreted in the urine was 1.7% of the administered dose. 50% of the activity was eliminated within 96 hours in the faeces.

Dose in renal impairment GFR (mL/min)

25–50	Dose as in normal renal function.
10–25	Avoid.
<10	Avoid.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Unknown dialysability. Avoid.
HD	Unknown dialysability. Avoid. See 'Other information'.
HDF/High flux	Unknown dialysability. Avoid. See 'Other information'.
CAV/VVHD	Unknown dialysability. Avoid.

Important drug interactions

Potentially hazardous interactions with other drugs

- Antibacterials: hypoglycaemic effect possibly enhanced and increased gastrointestinal side effects with neomycin.
- Lipid lowering agents: hypoglycaemic effect possibly enhanced by colestyramine.

Administration

Reconstitution

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Route

Oral

Rate of administration

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Other information

- Only 1–2% of active drug is absorbed.
- In renal impairment, peak concentrations are 5 times higher than in the general population and the AUC is 6 times higher.
- Manufacturer advises to avoid if GFR<25 mL/min due to lack of studies.
- One paper records the use of acarbose in a haemodialysis patient who had undergone a total gastrectomy to treat oxyhyperglycaemia: using a dose of 100 mg before meals. (Teno S, Nakajima-Uto Y, Nagai K, *et al*. Treatment with α-glucosidase inhibitor for severe reactive hypoglycemia. A case report. *Endocr J*. 2000; **47**(4): 437–42.

Acebutolol

Clinical use

Beta-adrenoceptor blocker:

- Hypertension
- Angina
- Arrhythmias

Dose in normal renal function

- Hypertension: 400 mg once a day or 200 mg twice a day, increased after 2 weeks to 400 mg twice daily if necessary
- Angina: 400 mg once a day, or 200 mg twice daily initially. Increase up to 300 mg 3 times daily; maximum 1200 mg
- Arrhythmias: 400–1200 mg/day (in 2–3 divided doses)

Pharmacokinetics

Molecular weight (daltons)	336.4 (372.9 as hydrochloride)
% Protein binding	26
% Excreted unchanged in urine	55
Volume of distribution (L/kg)	1.2
Half-life — normal/ESRF (hrs)	3–4 (8–13 for active metabolite) / Increased (32 for active metabolite)

Metabolism

After oral administration, there is rapid formation of a major equiactive metabolite, diacetolol, which possesses a similar pharmacological profile to acebutolol. Peak plasma concentrations of active material (i.e. acebutolol plus diacetolol) are achieved within 2–4 hours and the terminal plasma elimination half-life is around 8–10 hours. Because of biliary excretion and direct transfer across the gut wall from the systemic circulation to the gut lumen, more than 50% of an oral dose of acebutolol is recovered in the faeces with acebutolol and diacetolol in equal proportions; the rest of the dose is recovered in the urine, mainly as diacetolol.

Dose in renal impairment GFR (mL/min)

25–50	50% of normal dose, but frequency should not exceed once daily.
10–25	50% of normal dose, but frequency should not exceed once daily.
<10	25–50% of normal dose, but frequency should not exceed once daily.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Unknown dialysability. Dose as in GFR<10 mL/min.
HD	Dialysed. Dose as in GFR<10 mL/min.
HDF/High flux	Dialysed. Dose as in GFR<10 mL/min.
CAV/VVHD	Dialysed. Dose as in GFR=10–25 mL/min.

Important drug interactions

Potentially hazardous interactions with other drugs

- Anaesthetics: enhanced hypotensive effect.
- Analgesics: NSAIDs antagonise hypotensive effect.
- Anti-arrhythmics: increased risk of myocardial depression and bradycardia; increased risk of bradycardia, myocardial depression and AV block with amiodarone; increased risk of myocardial depression and bradycardia with flecainide.
- Antidepressants: enhanced hypotensive effect with MAOIs.
- Antihypertensives: enhanced hypotensive effect; increased risk of withdrawal hypertension with clonidine; increased risk of first dose hypotensive effect with post-synaptic alpha-blockers such as prazosin.
- Antimalarials: increased risk of bradycardia with mefloquine.
- Antipsychotics enhanced hypotensive effect with phenothiazines.
- Calcium-channel blockers: increased risk of bradycardia and AV block with diltiazem; hypotension and heart failure possible with nifedipine and nisoldipine; asystole, severe hypotension and heart failure with verapamil.
- Cytotoxics: possible increased risk of bradycardia with crizotinib.
- Diuretics: enhanced hypotensive effect.
- Fingolimod: possibly increased risk of bradycardia.

- Moxisylyte: possible severe postural hypotension.
- Sympathomimetics: severe hypertension with adrenaline and noradrenaline and possibly with dobutamine.

Administration

Reconstitution
—

Route
Oral

Rate of administration
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Other information

- Administration of high doses in severe renal failure cautioned due to accumulation.
- Doses from Sani M. Clinical pharmacology in the ICU. (1994); Section 1: p 64 and *Drug Prescribing in Renal Failure,* 5th edition by Aronoff *et al.*
- Dose frequency should not exceed once daily in renal impairment.
- Has an active metabolite – diacetolol.

Aceclofenac

Clinical use

NSAID and analgesic

Dose in normal renal function

100 mg twice daily

Pharmacokinetics

Molecular weight (daltons)	354.2
% Protein binding	>99
% Excreted unchanged in urine	66 (mainly as metabolites)
Volume of distribution (L/kg)	25 Litres
Half-life — normal/ESRF (hrs)	4 / Unchanged

Metabolism

About two-thirds of a dose is excreted in the urine, mainly as hydroxymetabolites, the principal one being 4-hydroxyaceclofenac. A small amount is converted to diclofenac.

Dose in renal impairment GFR (mL/min)

20–50	Dose as in normal renal function but use with caution.
10–20	Dose as in normal renal function but avoid if possible.
<10	Dose as in normal renal function but only if on dialysis.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Not dialysed. Dose as in normal renal function. See 'Other information'.
HD	Not dialysed. Dose as in normal renal function. See 'Other information'.
HDF/High flux	Unknown dialysability. Dose as in normal renal function. See 'Other information'.
CAV/VVHD	Not dialysed. Dose as in normal renal function.

Important drug interactions

Potentially hazardous interactions with other drugs

- ACE inhibitors and angiotensin-II antagonists: antagonism of hypotensive effect; increased risk of nephrotoxicity and hyperkalaemia.
- Analgesics: avoid concomitant use of 2 or more NSAIDs, including aspirin (increased side effects); avoid with ketorolac (increased risk of side effects and haemorrhage).
- Antibacterials: possible increased risk of convulsions with quinolones.
- Anticoagulants: effects of coumarins and phenindione enhanced; possibly increased risk of bleeding with heparins, dabigatran and edoxaban – avoid long term use with edoxaban.
- Antidepressants: increased risk of bleeding with SSRIs and venlaflaxine.
- Antidiabetic agents: effects of sulphonylureas enhanced.
- Antiepileptics: possibly increased phenytoin concentration.
- Antivirals: increased risk of haematological toxicity with zidovudine; concentration possibly increased by ritonavir.
- Ciclosporin: may potentiate nephrotoxicity
- Cytotoxics: reduced excretion of methotrexate; increased risk of bleeding with erlotinib.
- Diuretics: increased risk of nephrotoxicity; antagonism of diuretic effect, hyperkalaemia with potassium-sparing diuretics.
- Lithium: excretion decreased.
- Pentoxifylline: increased risk of bleeding.
- Tacrolimus: increased risk of nephrotoxicity.

Administration

Reconstitution

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Route

Oral

Rate of administration

—

Other information

- Use with caution in uraemic patients predisposed to gastrointestinal bleeding or uraemic coagulopathies.
- Inhibition of renal prostaglandin synthesis by NSAIDs may interfere with renal function, especially in the presence of existing renal disease – avoid if possible; if not, check serum creatinine 48–72 hours after starting NSAID therapy – if raised, discontinue NSAID therapy.
- Use normal doses in patients with ESRD on dialysis if they do not pass any urine.
- Use with great caution in renal transplant recipients; it can reduce intrarenal autocoid synthesis.

A

Acenocoumarol (nicoumalone)

Clinical use

Anticoagulant

Dose in normal renal function

- Initially: 2–4 mg on 1st day without a loading dose;
- Loading dose: 6 mg on 1st day then 4 mg on 2nd day
- Maintenance dose usually 1–8 mg daily according to INR

Pharmacokinetics

Molecular weight (daltons)	353.3
% Protein binding	>98
% Excreted unchanged in urine	<0.2
Volume of distribution (L/kg)	0.16–0.18 R(+) enantiomer; 0.22–0.34 S(–) enantiomer
Half-life — normal/ESRF (hrs)	8–11 / Probably unchanged

Metabolism

Acenocoumarol is extensively metabolised, although the metabolites appear to be pharmacologically inactive in man. 29% is excreted in the faeces and 60% in the urine, with less than 0.2% of the dose being renally excreted unchanged.

Dose in renal impairment GFR (mL/min)

20–50	Dose as in normal renal function.
10–20	Dose as in normal renal function.
<10	Dose as in normal renal function.

Dose in patients undergoing renal replacement therapies

APD/CAPD	Unknown dialysability. Dose as in normal renal function.
HD	Unknown dialysability. Dose as in normal renal function.
HDF/High flux	Unknown dialysability. Dose as in normal renal function.
CAV/VVHD	Unknown dialysability. Dose as in normal renal function.

Important drug interactions

Potentially hazardous interactions with other drugs

There are many significant interactions with coumarins. Prescribe with care with regard to the following:

- Anticoagulant effect enhanced by: alcohol, amiodarone, anabolic steroids, aspirin, aztreonam, bicalutamide, cephalosporins, chloramphenicol, cimetidine, ciprofloxacin, fibrates, clopidogrel, cranberry juice, danazol, dipyridamole, disulfiram, dronedarone, esomeprazole, ezetimibe, fibrates, fluconazole, flutamide, fluvastatin, grapefruit juice, itraconazole, ketoconazole, levamisole, levofloxacin, macrolides, methylphenidate, metronidazole, miconazole, nalidixic acid, neomycin, norfloxacin, NSAIDs, ofloxacin, omeprazole, pantoprazole, paracetamol, penicillins, propafenone, ritonavir, rosuvastatin, SSRIs, simvastatin, sulfinpyrazone, sulphonamides, tamoxifen, testosterone, tetracyclines, thyroid hormones, tigecycline, toremifene, tramadol, trimethoprim, valproate, vitamin E, voriconazole.
- Anticoagulant effect decreased by: acitretin, azathioprine, carbamazepine, enteral feeds, enzalutamide, fosphenytoin, griseofulvin, oral contraceptives, phenobarbital, phenytoin, primidone, rifamycins, St John's wort (avoid), sucralfate, vitamin K.
- Anticoagulant effects enhanced / reduced by: anion exchange resins, corticosteroids, dietary changes, efavirenz, fosamprenavir, tricyclics.
- Analgesics: increased risk of bleeding with IV diclofenac and ketorolac – avoid concomitant use.
- Anticoagulants: increased risk of haemorrhage with apixaban, dabigatran, edoxaban and rivaroxaban – avoid.
- Antidiabetic agents: enhanced hypoglycaemic effect with sulphonylureas also possible changes to anticoagulant effect.
- Ciclosporin: there have been a few reports of altered anticoagulant effect; decreased ciclosporin levels have been seen rarely.
- Cytotoxics: increased risk of bleeding with erlotinib; enhanced anticoagulant effect with capecitabine, etoposide, fluorouracil, ifosfamide, sorafenib and tegafur; reduced effect with mercaptopurine and mitotane.

Administration

Reconstitution

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Route

Oral

Rate of administration

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Other information

- Acenocoumarol prolongs the thromboplastin time within approximately 36–72 hours.
- Decreased protein binding in uraemia.
- Titrate dose to INR.
- Company advises to avoid in severe renal disease due to increased risk of haemorrhage if risk is greater than benefit.