

Frusemide-Claris

Frusemide Solution for Injection 10 mg/mL

Presentation

Frusemide-Claris is a clear colourless solution for injection containing 10 mg/mL frusemide (furosemide). It is available in 2 mL and 5 mL ampoules which contain 20 mg/2 mL and 50 mg/5 mL respectively.

Uses

Actions

Frusemide is a potent diuretic with a rapid action. It inhibits sodium and chloride absorption in the ascending limb of Henle's loop and in both the proximal and distal tubules. The high degree of efficacy is due to this unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase or aldosterone.

Frusemide may promote diuresis in cases which have previously proved resistant to other diuretics.

Frusemide has no significant pharmacological effects other than on renal function.

Pharmacokinetics

Absorption

Frusemide is rapidly absorbed from the gastrointestinal tract. Absorption rates in healthy subjects have been reported from 60 - 69 % and from 43 - 46 % in patients with end stage renal failure.

The onset of diuresis following intravenous administration is within 5 minutes and somewhat later after intramuscular administration. The peak effect occurs within the first half hour. The duration of diuretic effect is approximately 2 hours.

Distribution

Frusemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 - 400 µg/mL are 91 - 99% bound in healthy individuals. The unbound fraction averages 2.3 - 4.1% at therapeutic concentrations.

Metabolism

Recent evidence suggests that frusemide glucuronide is the only, or at least the major, bio-transformation product of frusemide in man.

Excretion

In patients with normal renal function, approximately 80% of an intravenous or intramuscular dose is excreted in the urine within 24 hours. Urinary excretion is accomplished both by glomerular filtration and proximal tubular secretion, which accounts for roughly 66% of the ingested dose, the remainder being excreted in the faeces. A small fraction is metabolised by cleavage of the side chain.

Significantly more frusemide is excreted in urine following the IV injection than after oral administration.

Frusemide has a biphasic half life in the plasma with $T_{1/2}$ ranging up to 100 minutes; $T_{1/2}$ is prolonged by renal and hepatic insufficiency and in new born infants.

Indications

Oedema

Frusemide-Claris Injection is indicated in adults, infants and children for the treatment of oedema associated with congestive heart failure, cirrhosis of the liver and renal disease including the nephrotic syndrome.

Frusemide is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired. Parenteral therapy should be reserved for patients unable to take oral medication or for patients in emergency clinical situations.

Frusemid-Claris Injection is also indicated as adjunctive therapy in acute pulmonary oedema and cerebral oedema where intense and rapid onset of diuresis is desired. If gastrointestinal absorption is impaired or oral medication is not practical for any reason, frusemide is indicated by the intravenous route. Parenteral use should be replaced with oral frusemide as soon as practical.

Dosage and Administration

Adults:

Parenteral therapy with Frusemide-Claris injection should be used only in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical.

Oedema:

The usual initial dose of Frusemide-Claris is 20 to 40 mg given as a single dose, injected intramuscularly or intravenously. The intravenous dose should be given slowly (see precautions). Ordinarily a prompt diuresis ensues. If needed, another dose may be administered in the same manner 2 hours later, or the dose may be increased. The dose may be raised by 20 mg, and given not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily.

Therapy should be individualised according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response. Close medical supervision is necessary. If the physician elects to use high dose parenteral therapy, add the Frusemide-Claris to either Sodium Chloride Injection or Lactated Ringer's Injection, and administer as a controlled intravenous infusion at a rate not greater than 4 mg/min. Frusemide-Claris Injection is a buffered alkaline solution.

Acute Pulmonary Oedema:

The usual initial dose of Frusemide-Claris is 40 mg injected slowly intravenously (see precautions). If a satisfactory response does not occur within 1 hour, the dose may be increased to 80 mg injected slowly intravenously. If necessary, additional therapy (e.g. digitalis, oxygen) may be administered concomitantly.

Cerebral Oedema:

The following procedure is recommended, pending further experience:

Intravenous injection of 20 to 40 mg three times daily. A more uniform diuretic action is obtained if the same doses are infused. The rate of infusion must be determined individually in accordance with the diuretic action and the neurological findings.

Infants and Children:

Parenteral therapy should be used only in patients unable to take oral medication or in emergency situations, and should be replaced with oral therapy as soon as practical.

The recommended dose of Frusemide-Claris Injection (intravenously or intramuscularly) in infants and children is 1 mg/kg body weight and should be given slowly under close medical supervision. If the diuretic response to the initial dose is not satisfactory, dosage may be increased by 1 mg/kg not sooner than 2 hours after the previous dose, until the desired effect has been obtained. Doses of greater than 6 mg/kg body weight are not recommended.

Frusemide-Claris Injection should be inspected visually for particulate matter and discolouration before administration. Do not use if solution is discoloured.

Frusemide-Claris is for single use in one patient only. Discard any residue.

Although the chemical stability of diluted Frusemide-Claris Injection has been demonstrated for storage at 25°C for 24 hours, the diluted solution should be used as soon as practicable to reduce risk of microbiological hazard. If storage is necessary hold the diluted solution at 2-8°C for not more than 24 hours.

Contraindications

- Known hypersensitivity to frusemide or sulfonamides or any of the inactive ingredients. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonyleureas) may show cross-sensitivity to Frusemide.
- Complete renal shutdown.
- If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, discontinue frusemide.
- Severe hypokalaemia, hyponatraemia, hypovolaemia or hypotension must be regarded as contraindications until serum electrolytes, fluid balance and blood pressure have been restored to normal levels.
- In hepatic coma or precoma and conditions producing electrolyte depletion, frusemide therapy should not be instituted until the underlying conditions have been corrected or ameliorated.
- In breast-feeding women.
- Do not administer frusemide to newborns presenting jaundice or to infants with conditions which might induce hyperbilirubinaemia or kernicterus (e.g. Rhesus incompatibility, familial non-haemolytic jaundice etc.) because of frusemide's 'in vitro' potential to displace bilirubin from albumin.
- Frusemide-Claris 250 mg injection must not be used as a bolus injection. It must only be infused using volume or rate controlled infusion pumps to reduce the risk of accidental overdose.

Warnings and Precautions

Excessive diuresis may result in dehydration and reduction in blood volume with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Excessive loss of potassium in patients receiving cardiac glycosides may precipitate digitalis toxicity.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Frusemide is best carried out in hospital.

Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma, therefore, strict observation is necessary during the period of diuresis.

Cases of reversible or irreversible tinnitus or hearing impairment have been reported. Usually, reports indicate that frusemide ototoxicity is associated with rapid injection or infusion, severe renal impairment, hypoproteinaemia, doses exceeding several times the usual recommended dose, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs. In patients with hypoproteinaemia, e.g. associated with nephrotic syndrome, the effect of frusemide may be weakened and its ototoxicity potentiated. Cautious dose titration is required. If the physician elects to use high dose parenteral therapy, controlled intravenous infusion is advisable (for adults with normal renal function, an infusion rate not exceeding 4 mg frusemide per minute must be used; for adults with impaired renal function [creatinine > 5 mg/dL], an infusion rate of no greater than 2.5 mg per minute must be used).

Caution should be exercised when administering curare or its derivatives to patients undergoing frusemide therapy. It is also advisable to discontinue frusemide for one week prior to any elective surgery.

Rigid sodium restriction is conducive to both hyponatraemia and hypokalaemia, thus strict restriction of sodium intake is not advisable in patients receiving frusemide.

Frusemide should be used with care, especially in the initial stages, in patients with impairment of micturition (e.g. prostatic hypertrophy). Urinary outflow must be secured. In patients with a partial obstruction of urinate outflow (e.g. in patients with bladder emptying disorders, prostatic hyperplasia or narrowing of the urethra), increased production of urine may provoke or aggravate complaints. These patients require careful monitoring.

Careful monitoring is required in patients with gout, with partial obstruction of urinary outflow, in patients at risk from hypotension (e.g. patients with coronary artery stenosis), in patients with latent or manifest diabetes mellitus, in patients with hepatorenal syndrome or in patients with hypoproteinaemia (e.g. associated with nephrotic syndrome). Dose titration, especially in this latter case, is required.

In premature infants, there is the possible development of nephrocalcinosis/nephrolithiasis and therefore renal function must be monitored and renal ultrasonography performed.

In premature infants frusemide administered during the first weeks of life may increase the risk of persistence of Botallo's duct.

As with any effective diuretic, electrolyte depletion may occur during therapy, especially in patients receiving higher doses and a restricted salt intake. All patients receiving frusemide therapy should be observed for signs of fluid or electrolyte imbalance; namely hyponatraemia, hypochloaemic alkalosis, and hypokalaemia. Periodic determinations of serum electrolytes to detect a possible imbalance should be performed at appropriate intervals, as well as creatinine, blood urea and CO₂ content determinations. This is particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs of an imbalance, irrespective of cause include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, and gastrointestinal disturbances such as nausea and vomiting. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of frusemide.

During long-term therapy, a high potassium diet is recommended. Potassium supplements may be required, especially when high doses are used for prolonged periods. Particular caution with potassium is necessary when the patient is on digitalis glycosides, potassium depleting steroids or in the case of infants and children. Potassium supplementation, diminution in dose, or discontinuation of frusemide therapy may be required.

Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving frusemide. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and 2-hour post prandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Frusemide may lower calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

In children, urge to defecate, complaints of abdominal pain and cramping have been reported after IV Frusemide. An association of these symptoms with a low serum calcium and/or a low calcium/protein ratio is possible.

Reversible elevations of blood urea may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Furosemide increases cholesterol and triglycerides short-term. It is not clear whether this effect persists long-term, however, the current evidence does not indicate this.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

Renal calcifications (from barely visible on X-ray to staghorn) have occurred in some severely premature infants treated with intravenous furosemide for oedema due to patent ductus arteriosus and hyaline membrane disease. The concurrent use of chlorothiazides has been reported to decrease hypercalciuria and to dissolve some calculi.

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

Asymptomatic hyperuricaemia can occur and rarely, gout may be precipitated.

When furosemide is administered parenterally, a maximum injection rate of 4 mg/minute should be used to minimise the risk of ototoxicity.

Intramuscular administration of furosemide must be limited to exceptional cases where neither oral nor intravenous administration are feasible. Intramuscular administration is not suitable for acute conditions such as pulmonary oedema.

Use during Pregnancy and Lactation

Category C

Furosemide must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics, like furosemide and bumetanide, are probably also associated with this risk. During the latter part of pregnancy, products of this type should only be given on sound indications, and then in the lowest effective dose. In pregnancy, furosemide must only be used in patients with a marked reduction in glomerular filtration.

Furosemide passes into the breast milk and inhibits lactation. Women must not breast feed if being treated with furosemide.

Effects on ability to drive and use machines

Some adverse effects (e.g. an undesirable pronounced fall in blood pressure) may impair the patient's ability to concentrate and react and therefore constitute a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

Adverse Effects

As with other diuretics, electrolytes and water balance may be disturbed during therapy with furosemide, especially in patients receiving high doses for a prolonged period.

Excessive diuresis may give rise, especially in elderly patients and children, to circulatory disturbances such as headache, dizziness, dry mouth or visual impairment, as symptoms of hypovolaemia. In extreme cases, hypovolaemia and dehydration may lead to hypotension, circulatory collapse and, in elderly patients in particular, thrombophilia. However, with individualised dosage, acute haemodynamic reactions are generally not to be expected, although diuresis sets in rapidly.

All saluretics may cause hypokalaemia, mainly in cases of low potassium diet, vomiting or chronic diarrhoea.

Factors such as underlying diseases (liver cirrhosis, cardiac failure), concomitant medication or nutritional inadequacies (excessive restriction of salt intake), may lead to sodium or other electrolyte or fluid deficiencies which may produce a fall in

orthostatic blood pressure, calf muscle spasms, anorexia, weakness, dizziness, drowsiness, apathy, vomiting and confusion.

Furosemide may lower the serum calcium level which may trigger a state of increased neuromuscular irritability. In very rare cases, tetany has been observed. In premature infants, calcium salts may be deposited in the renal tissue (nephrocalcinosis).

Hypomagnesaemia and, in rare cases, tetany or cardiac arrhythmias have been observed as a consequence of increased renal magnesium loss.

Treatment with furosemide may lead to transitory increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

Pre-existing metabolic alkalosis (e.g. due to decompensated liver cirrhosis) may be aggravated during furosemide treatment.

Hepatic System

In isolated cases, acute pancreatitis and increases in liver transaminases have been observed. Additionally, intrahepatic cholestasis and jaundice have been reported. Furosemide may increase the bile flow and distend the biliary tree which is already obstructed.

Central Nervous System

Reactions such as dizziness, vertigo, paraesthesia, headache and blurred vision occasionally accompany furosemide induced diuresis. Reversible hearing impairment and tinnitus and rarely, permanent tinnitus and impairment of hearing have been observed, especially in patients with markedly reduced renal function or hypoproteinaemia (e.g. in nephrotic syndrome). This occurs particularly when the recommended rate of injection or infusion of 4 mg per minute (normal renal function) or 2.5 mg per minute (impaired renal function) is exceeded, or in patients who are also receiving drugs known to be ototoxic.

Dermatologic

Allergic reactions may occur in the form of dermatitis, including rash, urticaria and rare cases of exfoliative dermatitis, necrotising angitis, bullous eruptions, erythema multiforme and purpura and pruritus. Photosensitivity reactions have been reported.

Haematologic

The following rare adverse reactions have been reported: eosinophilia, thrombophlebitis, haemolytic or aplastic anaemia, leukopaenia, thrombocytopaenia and agranulocytosis. Vasculitis may also occur.

Urinary System

Excessive diuresis and dehydration could cause transient elevation of creatinine and BUN and reduction of GFR. In elderly men with prostatic hypertrophy, acute urinary retention with overflow incontinence may occur. Symptoms of existing conditions of obstructed micturition, such as uretostenosis or hydronephrosis, may be triggered or aggravated by pronounced diuresis. Interstitial nephritis has also been reported with Furosemide use.

Cardiovascular

Orthostatic hypotension may occur and may be aggravated by alcohol, narcotics and barbiturates. Ischaemic complications have also been reported in elderly patients.

Other

Restlessness, hyperuricaemia, fever, a rise in serum cholesterol and triglyceride,

In patients with hepatocellular insufficiency, hepatic encephalopathy may occur.

Treatment with furosemide has occasionally caused reduced glucose tolerance and deterioration in cases of manifest diabetes, or made latent diabetes manifest.

Rarely, fever or paraesthesiae and occasionally photosensitivity may occur.

In premature infants, furosemide may precipitate nephrocalcinosis/nephrolithiasis. If Furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Following intramuscular injection, local reactions such as pain may occur.

Due to the possibility of side effects such as hypotension, patients' ability to drive or operate machinery may be impaired, especially at the commencement of therapy. Anaphylactic shock is rare, but is acutely life-threatening if it does occur. Whenever adverse reactions are moderate or severe, frusemide dose should be reduced or therapy withdrawn.

Interactions

Combinations that are not recommended

Frusemide may increase the ototoxic and nephrotoxic potential of certain antibiotics (e.g. aminoglycosides and certain cephalosporins (e.g. cephaloridine), especially in the presence of impaired renal function, therefore the simultaneous administration of these drugs is not advisable.

Anticonvulsants may decrease the response to frusemide. In isolated cases intravenous administration of frusemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, tachycardia and elevation of blood pressure. As a result, this combination is not recommended.

Precautions for Use

Frusemide should not be used concomitantly with ethacrynic acid or cisplatin because of the possibility of ototoxicity. In addition, nephrotoxicity of cisplatin may be enhanced if frusemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Frusemide decreases the excretion of lithium salts and may cause increased serum lithium levels resulting in increased risk of lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. It is recommended that lithium levels are carefully monitored in patients receiving this combination.

Administration of frusemide and sucralfate within two hours of each other should be avoided, as sucralfate reduces the absorption of frusemide and hence, reduces its effect.

The action of other antihypertensive drugs may be potentiated by frusemide, especially in combination with ACE inhibitors. The administration of ACE inhibitors to patients pretreated with frusemide may lead to a deterioration in renal function or may result in severe hypotension especially when an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor antagonist is given for the first time or for the first time in an increased dose. Consideration must be given to interrupting the administration of frusemide temporarily or at least reducing the dose of frusemide for 3 days before starting treatment with an ACE inhibitor or increasing the dose of the ACE inhibitor or angiotensin II receptor antagonist.

To be considered

The effects of digitalis preparations and drugs inducing QT interval prolongation syndrome may be potentiated by changes in electrolyte concentrations e.g. hypokalaemia, hypomagnesaemia due to frusemide. When a cardiac glycoside is administered concurrently, it should be remembered that potassium or magnesium deficiency increases the sensitivity of the myocardium to digitalis and may increase the toxicity of drugs which induce QT interval prolongation syndrome. When a glucocorticoid is administered during diuretic treatment, the potassium-lowering effect of the steroid should be borne in mind. Carbenoxolone, corticosteroids, prolonged use of laxatives or ingestion of liquorice in large amounts may also predispose a patient to hypokalaemia.

Patients receiving high doses of salicylates, as in rheumatic disease, in conjunction with frusemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Interactions between frusemide and neuromuscular blocking agents have been reported. These appear to be dependent on the dose of frusemide and the

neuromuscular blocking agent involved. Low doses of frusemide (0.1-10 µg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1-5mg/kg) of frusemide have a tendency to antagonise the skeletal muscle relaxing effect of tubocurarine but may potentiate the action of succinylcholine. The clinical relevance of these findings is uncertain.

The combination of frusemide and amphotericin may result in an excessive loss of potassium.

Frusemide may decrease arterial responsiveness to noradrenaline. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If antihypertensive agents, diuretics or other drugs with blood-pressure lowering potential are given concomitantly with frusemide, a more pronounced fall in blood pressure must be anticipated.

Non-steroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the natriuretic and antihypertensive effects of frusemide in some patients by inhibiting prostaglandin synthesis. In patients with dehydration or pre-existing hypovolaemia, non-steroidal anti-inflammatory drugs may cause renal failure. Salicylate toxicity may be increased by frusemide.

Phenytoin or drugs which undergo significant renal tubular secretion such as methotrexate and probenecid, may attenuate the effects of frusemide. Conversely frusemide may decrease renal elimination of these drugs. In the case of high dose treatment (in particular of both frusemide and the other drugs), this may lead to an increased risk of adverse effects due to frusemide or the concomitant medication.

IV Frusemide was shown to increase the steady state concentration of theophylline by 20% in a small number of asthmatic patients; hence it is appropriate to measure serum theophylline levels when both drugs are given together.

The effects of curare-type muscle relaxants or of theophylline may be increased.

It should be borne in mind that the effect of antidiabetics or of pressor amines (e.g. adrenaline, noradrenaline) may be attenuated by frusemide.

Impairment of renal function may develop in patients receiving concurrent treatment with frusemide and high doses of certain cephalosporins. The harmful effects of nephrotoxic drugs on the kidney may be increased.

Concomitant use of cyclosporine A and frusemide is associated with increased risk of gouty arthritis secondary to frusemide-induced hyperuricemia and cyclosporine impairment of renal urate excretion.

Patients who were at high risk for radiocontrast nephropathy treated with frusemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patient who received only intravenous hydration prior to receiving radiocontrast.

Overdosage

Symptoms

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss; e.g. dehydration, blood volume reduction, hypotension, electrolyte imbalance, cardiac arrhythmias (including A-V block and ventricular fibrillation), hypokalaemia and hypochloraemic alkalosis, and extensions of its diuretic action. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

The acute toxicity of frusemide has been determined in mice, rats and dogs. In all three, the oral LD50 exceeded 1 000 mg/kg body weight, while the intravenous LD50 ranged from 300 to 680 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats. The concentration of frusemide in biological fluids associated with toxicity or death is not known.

Treatment

No specific antidote to frusemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as activated charcoal.

Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy). Haemodialysis does not accelerate frusemide elimination.

Contact the Poisons Information Centre (Telephone 13 11 26) for advice on management of overdosage.

Pharmaceutical Precautions

Store below 30°C. Protect from light. Occasionally crystal deposits may be seen when Frusemide-Claris ampoules are stored at low temperatures. Dissolve crystals by warming to 40°C and injection may be used.

Although the chemical stability of diluted Frusemide-Claris has been demonstrated for storage at 25 °C for 24 hours, the diluted solution should be used as soon as practicable to reduce the risk of microbiological hazard. If storage is necessary, hold the diluted solution at 2-8 °C (under refrigeration) for not more than 24 hours.

Medicines Classification

Prescription Medicine

Package Quantities

Frusemide-Claris ampoules, 20 mg/2 mL; 50 mg/5 mL: packs of 5 and 25 ampoules.

Further Information

Inactive ingredients: sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

Name and Address

AFT Pharmaceuticals Ltd
9 Anzac Street (Level 2)
Takapuna
Auckland
Email: customer.service@aftpharm.com

Date of Preparation

22 April 2009