SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aminophylline Injection BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 25mg of Aminophylline Ph Eur

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Disease of the cardiovascular system (e.g. an adjunct in the treatment of pulmonary oedema or paroxysmal nocturnal dyspnoea caused by left ventricular heart failure), reversible airways obstruction including status asthmaticus and acute bronchospasm.

4.2 Posology and method of administration

Aminophylline has a narrow therapeutic index, therefore cautious dosage determination is essential. Therapeutic serum concentrations of theophylline are considered to range from 10 to 20 micrograms/ml and levels greater than 20 micrograms/ml are often associated with toxic effects. A range of 5 to 15 micrograms/ml may be effective, and associated with fewer adverse effects.

The dosage should be titrated for each individual and adjusted with caution. Serum theophylline levels should be monitored to ensure that they remain within the therapeutic range. During therapy, patients should be monitored carefully for signs of toxicity.

Elimination of theophylline in children younger than 6 months of age, especially in neonates, appears to be reduced. Because of this variation in metabolism the use of Aminophylline injection in children under 6 months of age is not recommended.

Use in patients NOT currently receiving theophylline preparations

To minimise adverse effects, IV Aminophylline should be administered slowly, at a rate not exceeding 25mg Aminophylline per minute, up to a dose of 250-500mg (5mg/kg). If patients experience acute adverse effects while loading doses are being infused, the infusion may be stopped for 5-10 minutes or administered at a slower rate.

Approximate IV Aminophylline Maintenance Doses

n.b. The use of Aminophylline IV in children under 6 months of age is not recommended.

Group	Maintenance Dose
Children 6 months to 9 years of age	1mg/kg/hour
Children 10-16 years of age and young adult smokers	0.8mg/kg/hour
Otherwise healthy non-smoking adults	0.5mg/kg/hour
Elderly patients	0.3mg/kg/hour

Use in patients currently receiving theophylline preparations

In patients who are currently receiving theophylline preparations, the time, route of administration and dosage form of the patient's last dose should be determined where possible and considered in determining a loading dose.

Loading doses are based on the expectation that 0.5mg/kg (lean body weight) of theophylline will result in a 1 microgram/ml increase in serum theophylline concentration.

Therefore, in patients currently receiving theophylline preparations, the loading dose should be deferred until a serum theophylline concentration can be attained or the clinician must carefully select a dose based on the potential benefits and risks.

Subsequently, the approximate IV aminophylline maintenance doses described above may be considered.

Method of administration

Aminophylline Injection BP may be given by slow intravenous injection or intravenous infusion in glucose injection or sodium chloride injection.

4.3 Contraindications

The use of Aminophylline is contraindicated in patients with hypersensitivity to ethylenediamine or those allergic to the theophyllines, caffeine or theobromine or to any of the excipients listed in section 6.1.

Aminophylline should not be administered concomitantly with other xanthine drugs. When therapeutic doses of Aminophylline and/or theophylline are administered simultaneously by more that one route or in more than one preparation, the hazard of serious toxicity is increased.

The use of Aminophylline IV in children under 6 months of age is not recommended.

The use of Aminophylline is contraindicated in patients with acute porphyria.

4.4 Special warnings and precautions for use

Intravenous Aminophylline must be administered very slowly to prevent dangerous central nervous system and cardiovascular side-effects due to direct stimulating effect of Aminophylline and should not exceed a rate of 25 mg/min (see section 4.2).

Aminophylline has a narrow therapeutic index and serum levels should be monitored regularly, particularly during initiation of therapy.

Aminophylline injection should be administered cautiously to patients over 55 years of age.

Children are particularly susceptible to the effects of theophylline and care is required when administrating aminophylline to children.
There have been reports of seizures in children with theophylline plasma levels within the accepted therapeutic range. Alternative treatment should be considered in patients with a history of seizure activity and, if Aminophylline Injection is used in such patients, they should be carefully observed for possible signs of central stimulation.

Caution is also advised in patients undergoing influenza immunisation or who have active influenza infection or acute febrile illness.

Aminophylline should be given with caution to patients with cardiac failure, chronic obstructive pulmonary disease, renal or hepatic dysfunction and in chronic alcoholism since clearance of Aminophylline is decreased.

Because the mean half-life of theophylline is shorter in smokers than in non-smokers, the former group may require larger doses of aminophylline.

During regular therapy serum potassium levels must be monitored. This is essential during combination therapy with beta2-agonists, corticosteroids or diuretics, or in the presence of hypoxia.

Aminophylline should be used with caution in patients with peptic ulcer, hyperthyroidism, glaucoma, diabetes mellitus, severe hypoxaemia, hypertension, compromised cardiac or circulatory function and epilepsy, as these conditions may be exacerbated.

Methylxanthines may increase gastric acidity and care should be taken when they are used in patients with a history of peptic ulceration

Aminophylline should not be administered concurrently with other xanthine medications.

4.5 Interactions with other medicinal products and other forms of interactions

The following drugs may **increase** plasma theophylline concentrations:

- Fluvoxamine

The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose halved and plasma theophylline should be monitored closely.

- Cimetidine
- Macrolide antibiotics (e.g. erythromycin, clarithromycin)
- Quinolone antibiotics (e.g. ciprofloxacin, norfloxacin)
- Fluconazole
- Isoniazid
- Propranolol
- Allopurinol (high doses e.g. 600 mg daily)
- Oral contraceptives
- Mexiletine, propafenone
- Calcium channel blockers, diltiazem, verapamil
- Disulfiram
- Interferon alfa, influenza vaccine
- Methotrexate
- Zafirlukast
- Tacrine
- Thiabendazole
- Thyroid hormones

The following drugs may **decrease** plasma theophylline concentrations:

- Rifampicin
- Antiepileptics (e.g. carbamazepine, phenytoin, primidone, phenobarbitone)
- Ritonavir
- Aminoglutethimide
- Sulfinpyrazone
- St John’s Wort (Hypericum perforatum)

Other interactions:

Xanthines
Concurrent use of other xanthine derivatives, including theophylline and pentoxifylline are contraindicated due to the risk of toxicity.

Lithium
Aminophylline increases the excretion of lithium and may decrease its therapeutic effectiveness.

Benzodiazepines:
Theophylline may reduce the effects of benzodiazepines.

Quinolones
Increased risk of convulsions.

General anaesthetics
Increased risk of convulsions with ketamine; increased risk of arrhythmias with halothane

Pancuronium
Resistance to neuromuscular block with pancuronium has been reported in patients receiving aminophylline.

Sympathomimetics
Aminophylline may exhibit synergistic toxicity with ephedrine and other sympathomimetics and concurrent use may dispose the patient to cardiac arrhythmias.

Beta$_2$-adrenergic agonists
Increased risk of cardiac arrhythmias (see also hypokalaemia).

Beta-blockers
Antagonism of bronchodilator effects.

Cardiac glycosides
The direct stimulatory effect of Aminophylline on the myocardium may enhance the sensitivity and toxic potential of the cardiac glycosides.

Adenosine
The anti-arrhythmic effect of adenosine is antagonised by theophylline.

Leukotriene antagonists
In clinical trials co-administration with theophylline resulted in decreased plasma levels of zafirlukast, by approximately 30%, but with no effect on plasma theophylline levels. However, during post-marketing surveillance, there have been rare cases of patients experiencing increased theophylline levels when co-administered zafirlukast (see above).

Doxapram
Increased CNS stimulation.

Hypokalaemia
The hypokalaemic effects of beta$_2$-adrenergic agonists may be potentiated by concomitant treatment with aminophylline. There is an increased risk of hypokalaemia when theophylline derivatives are given with corticosteroids or diuretics (see 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Pregnancy
It is not known whether theophyllines can cause foetal harm when administered to pregnant women. Although the safe use of theophylline during pregnancy has not been established relative to potential risk to the foetus, theophyllines have been used during pregnancy without teratogenicity or other adverse foetal effect. Because of the risk of uncontrolled asthma, their safety during pregnancy when clearly needed is generally not seriously questioned. As with other drugs, aminophylline should only be used during pregnancy if considered essential by the physician. Theophylline crosses the placenta.

Breast-feeding
Theophylline is distributed into milk and may occasionally induce irritability or other signs of toxicity in nursing infants, and therefore should not be used if the mother is breast-feeding her infant.

Fertility
Animal reproduction studies have not been performed with theophyllines.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Adverse events are usually a consequence of gastrointestinal irritation, stimulation of the central nervous system and effects on the cardiovascular system. Hypotension, arrhythmias and convulsions may follow intravenous injection, particularly if the injection is too rapid, and sudden deaths have been reported. Severe toxicity may occur without preceding milder symptoms (see also 4.9 Overdose).

Immune system disorders:
Hypersensitivity reactions (see also Skin and subcutaneous tissue disorders).

Metabolism and nutrition disorders:
Metabolic disturbances such as hypokalaemia, hypophosphataemia, and hyponatraemia may occur.

Psychiatric disorders:
Insomnia, anxiety. Higher doses may lead to maniacal behaviour, delirium and convulsions.

Nervous system disorders:
Headache, confusion, restlessness, hyperventilation, vertigo/dizziness, tremor.

Eye disorders:
Visual disturbances.

Cardiac disorders:
Palpitations, tachycardia, cardiac arrhythmias, hypotension.

Gastrointestinal disorders:
Nausea, vomiting, abdominal pain, diarrhoea, gastro-oesophageal reflux, gastrointestinal bleeding.

Skin and subcutaneous tissue disorders:
Rash, maculo-papular rash, erythema, pruritus, urticaria, exfoliative dermatitis.

General/Administration site reactions:
Higher doses may result in hyperthermia and extreme thirst. Intramuscular injections are painful, the pain lasting several hours.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Aminophylline has a narrow therapeutic index. Theophylline toxicity is most likely to occur when serum concentrations exceed 20 micrograms/ml and becomes progressively more severe at higher serum concentrations.

Fatalities in adults have occurred during IV Aminophylline administration in large doses in patients with renal, hepatic or cardiovascular complications or where the injection has been given rapidly.

Symptoms
Tachycardia, in the absence of hypoxia, fever or administration of sympathomimetic drugs, may be an indication of theophylline toxicity.

Gastro-intestinal symptoms:
Anorexia, nausea, vomiting, diarrhoea, and haematemesis.

Neurological symptoms:

Restlessness, insomnia, irritability, headache, agitation, hallucinations, extreme thirst, slight fever, dilated pupils, and tinnitus. Seizures may occur even without preceding symptoms of toxicity and often result in death. Coma may develop in very severe cases.

Cardiovascular symptoms:
Palpitations, arrhythmias, hypotension, supraventricular and ventricular arrhythmias may occur.

Metabolic symptoms:
Hypokalaemia can develop rapidly and may be severe. Hyperglycaemia, albuminuria, hyperthermia, hypomagnesaemia, hypophosphataemia, hypercalcaemia, respiratory alkalosis and metabolic acidosis may also occur. Rhabdomyolysis may also occur.

Treatment
Treatment of overdosage is supportive and symptomatic. Serum theophylline and potassium levels should be monitored. Repeated oral administration of activated charcoal enhances the elimination of theophylline from the body even after intravenous administration. Aggressive antiemetic therapy may be required to allow administration and retention of activated charcoal.

Seizures may be treated with IV diazepam 0.1-0.3mg/kg up to 10mg. Restoration of fluid and electrolytes balance is necessary. Hypokalaemia should be corrected by intravenous infusion of potassium chloride. Sedation with diazepam may be required in agitated patients.

Propranolol may be administered intravenously to reverse extreme tachycardia, hypokalaemia and hyperglycaemia provided the patient does not suffer from asthma.

In general, theophylline is metabolised rapidly and haemodialysis is not warranted. In patients with congestive heart failure or liver disease, haemodialysis may increase theophylline clearance by as much as 2-fold.

Charcoal haemoperfusion should be considered if:

- Ileus/ intestinal obstruction prevents administration of multiple dose activated charcoal.

- Plasma theophylline concentration > 80mg/L (acute) or > 60mg/L (chronic).

In infants under 6 months of age or the elderly, charcoal haemoperfusion should be considered at theophylline concentrations >40 mg/L. Clinical features rather than theophylline concentration are the best guide for treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Xanthines, ATC code: R03DA05

Mechanism of Action:
Aminophylline is a soluble derivative of theophylline and is given for its theophylline activity. Aminophylline relaxes smooth muscle and relieves bronchial spasm. It stimulates the myocardium and reduces venous pressure in congestive heart failure, leading to a marked increase in cardiac output. It has stimulant effect on respiration, and also a diuretic action of short duration.

5.2 Pharmacokinetic properties

Distribution:
Theophylline is approximately 60% bound to plasma proteins but binding is decreased to about 40% in neonates and in adults with hepatic disease. The drug is widely distributed and it crosses the placenta and passes into breast milk.

Biotransformation and Elimination:
Theophylline is metabolised in the liver and the metabolites are excreted in the urine. In adults, about 10% of a dose of theophylline is excreted unchanged in the urine. There is considerable inter-individual variation in the rate of hepatic metabolism of theophylline, resulting in large variations in clearance, serum concentrations and half-lives. Cigarette smoking increases theophylline clearance and shortens its serum half-life.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylenediamine Ph. Eur.
Water for Injections Ph. Eur.

6.2 Incompatibilities

Aminophylline injection is not stable in solutions having a pH of substantially less than 8, however, the drug appears to be relatively stable in large volume parenteral solutions over a wide pH range (3.5-8.6) if Aminophylline concentrations do not exceed 40mg per ml. The activity of alkali-sensitive drugs will be reduced by Aminophylline, these drugs should not be added to IV fluids containing Aminophylline.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

10ml clear glass ampoules, packed in cardboard cartons to contain 10 ampoules

6.6 Special precautions for disposal and other handling

Use as directed by a physician.

7. MARKETING AUTHORISATION HOLDER

hameln pharma ltd
Nexus, Gloucester Business Park
Gloucester, GL3 4AG
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 01502/0009R

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

12th February 1990/ 11th September 2002

10. DATE OF REVISION OF THE TEXT

4.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 25mg of Aminophylline Ph Eur

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Disease of the cardiovascular system (e.g. an adjunct in the treatment of pulmonary oedema or paroxysmal nocturnal dyspnoea caused by left ventricular heart failure), reversible airways obstruction including status asthmaticus and acute bronchospasm.

4.2 Posology and method of administration

Aminophylline has a narrow therapeutic index, therefore cautious dosage determination is essential. Therapeutic serum concentrations of theophylline are considered to range from 10 to 20 micrograms/ml and levels greater than 20 micrograms/ml are often associated with toxic effects. A range of 5 to 15 micrograms/ml may be effective, and associated with fewer adverse effects.

The dosage should be titrated for each individual and adjusted with caution. Serum theophylline levels should be monitored to ensure that they remain within the therapeutic range. During therapy, patients should be monitored carefully for signs of toxicity.

Elimination of theophylline in children younger than 6 months of age, especially in neonates, appears to be reduced. Because of this variation in metabolism the use of Aminophylline injection in children under 6 months of age is not recommended.

Use in patients NOT currently receiving theophylline preparations

To minimise adverse effects, IV Aminophylline should be administered slowly, at a rate not exceeding 25mg Aminophylline per minute, up to a dose of 250-500mg (5mg/kg). If patients experience acute adverse effects while loading doses are being infused, the infusion may be stopped for 5-10 minutes or administered at a slower rate.

Approximate IV Aminophylline Maintenance Doses

n.b. The use of Aminophylline IV in children under 6 months of age is not recommended.

Group	Maintenance Dose
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Children 10-16 years of age and young adult smokers	0.8mg/kg/hour
Otherwise healthy non-smoking adults	0.5mg/kg/hour
Elderly patients	0.3mg/kg/hour

Use in patients currently receiving theophylline preparations

In patients who are currently receiving theophylline preparations, the time, route of administration and dosage form of the patient's last dose should be determined where possible and considered in determining a loading dose.

Loading doses are based on the expectation that 0.5mg/kg (lean body weight) of theophylline will result in a 1 microgram/ml increase in serum theophylline concentration.

Therefore, in patients currently receiving theophylline preparations, the loading dose should be deferred until a serum theophylline concentration can be attained or the clinician must carefully select a dose based on the potential benefits and risks.

Subsequently, the approximate IV aminophylline maintenance doses described above may be considered.

Method of administration
Aminophylline Injection BP may be given by slow intravenous injection or intravenous infusion in glucose injection or sodium chloride injection.

4.3 Contraindications

The use of Aminophylline is contraindicated in patients with hypersensitivity to ethylenediamine or those allergic to the theophyllines, caffeine or theobromine or to any of the excipients listed in section 6.1.

Aminophylline should not be administered concomitantly with other xanthine drugs. When therapeutic doses of Aminophylline and/or theophylline are administered simultaneously by more that one route or in more than one preparation, the hazard of serious toxicity is increased.

The use of Aminophylline IV in children under 6 months of age is not recommended.

The use of Aminophylline is contraindicated in patients with acute porphyria.

4.4 Special warnings and precautions for use

Intravenous Aminophylline must be administered very slowly to prevent dangerous central nervous system and cardiovascular side-effects due to direct stimulating effect of Aminophylline and should not exceed a rate of 25 mg/min (see section 4.2).

Aminophylline has a narrow therapeutic index and serum levels should be monitored regularly, particularly during initiation of therapy.

Aminophylline injection should be administered cautiously to patients over 55 years of age.

Children are particularly susceptible to the effects of theophylline and care is required when administrating aminophylline to children.

There have been reports of seizures in children with theophylline plasma levels within the accepted therapeutic range. Alternative treatment should be considered in patients with a history of seizure activity and, if Aminophylline Injection is used in such patients, they should be carefully observed for possible signs of central stimulation.

Caution is also advised in patients undergoing influenza immunisation or who have active influenza infection or acute febrile illness.

Aminophylline should be given with caution to patients with cardiac failure, chronic obstructive pulmonary disease, renal or hepatic dysfunction and in chronic alcoholism since clearance of Aminophylline is decreased.

Because the mean half-life of theophylline is shorter in smokers than in non-smokers, the former group may require larger doses of aminophylline.

During regular therapy serum potassium levels must be monitored. This is essential during combination therapy with beta2-agonists, corticosteroids or diuretics, or in the presence of hypoxia.

Aminophylline should be used with caution in patients with peptic ulcer, hyperthyroidism, glaucoma, diabetes mellitus, severe hypoxaemia, hypertension, compromised cardiac or circulatory function and epilepsy, as these conditions may be exacerbated.

Methylxanthines may increase gastric acidity and care should be taken when they are used in patients with a history of peptic ulceration

Aminophylline should not be administered concurrently with other xanthine medications.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs may **increase** plasma theophylline concentrations:

- Fluvoxamine

The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose halved and plasma theophylline should be monitored closely.

- Cimetidine
- Macrolide antibiotics (e.g. erythromycin, clarithromycin)
- Quinolone antibiotics (e.g. ciprofloxacin, norfloxacin)
- Fluconazole
- Isoniazid
- Propranolol
- Allopurinol (high doses e.g. 600 mg daily)
- Oral contraceptives
- Mexiletine, propafenone
- Calcium channel blockers, diltiazem, verapamil

- Disulfiram
- Interferon alfa, influenza vaccine
- Methotrexate
- Zafirlukast
- Tacrine
- Thiabendazole
- Thyroid hormones

The following drugs may **decrease** plasma theophylline concentrations:

- Rifampicin
- Antiepileptics (e.g. carbamazepine, phenytoin, primidone, phenobarbitone)
- Ritonavir
- Aminoglutethimide
- Sulfinpyrazone
- St John's Wort (Hypericum perforatum)

Other interactions:

Xanthines
Concurrent use of other xanthine derivatives, including theophylline and pentoxifylline are contraindicated due to the risk of toxicity.

Lithium
Aminophylline increases the excretion of lithium and may decrease its therapeutic effectiveness.

Benzodiazepines:
Theophylline may reduce the effects of benzodiazepines.

Quinolones
Increased risk of convulsions.

General anaesthetics
Increased risk of convulsions with ketamine; increased risk of arrhythmias with halothane

Pancuronium
Resistance to neuromuscular block with pancuronium has been reported in patients receiving aminophylline.

Sympathomimetics
Aminophylline may exhibit synergistic toxicity with ephedrine and other sympathomimetics and concurrent use may dispose the patient to cardiac arrhythmias.

Beta$_2$-adrenergic agonists

Increased risk of cardiac arrhythmias (see also hypokalaemia).

Beta-blockers
Antagonism of bronchodilator effects.

Cardiac glycosides
The direct stimulatory effect of Aminophylline on the myocardium may enhance the sensitivity and toxic potential of the cardiac glycosides.

Adenosine
The anti-arrhythmic effect of adenosine is antagonised by theophylline.

Leukotriene antagonists
In clinical trials co-administration with theophylline resulted in decreased plasma levels of zafirlukast, by approximately 30%, but with no effect on plasma theophylline levels. However, during post-marketing surveillance, there have been rare cases of patients experiencing increased theophylline levels when co-administered zafirlukast (see above).

Doxapram
Increased CNS stimulation.

Hypokalaemia
The hypokalaemic effects of beta2-adrenergic agonists may be potentiated by concomitant treatment with aminophylline. There is an increased risk of hypokalaemia when theophylline derivatives are given with corticosteroids or diuretics (see 4.4 Special warnings and precautions for use).

4.10 Fertility, pregnancy and lactation

Pregnancy
It is not known whether theophyllines can cause foetal harm when administered to pregnant women. Although the safe use of theophylline during pregnancy has not been established relative to potential risk to the foetus, theophyllines have been used during pregnancy without teratogenicity or other adverse foetal effect. Because of the risk of uncontrolled asthma, their safety during pregnancy when clearly needed is generally not seriously questioned. As with other drugs, aminophylline should only be used during pregnancy if considered essential by the physician. Theophylline crosses the placenta.

Breast-feeding
Theophylline is distributed into milk and may occasionally induce irritability or other signs of toxicity in nursing infants, and therefore should not be used if the mother is breast-feeding her infant.

Fertility
Animal reproduction studies have not been performed with theophyllines

4.7. Effects on Ability to Drive and Use Machines

None known.

4.8 Undesirable effects

Adverse events are usually a consequence of gastrointestinal irritation, stimulation of the central nervous system and effects on the cardiovascular system. Hypotension, arrhythmias and convulsions may follow intravenous injection, particularly if the injection is too rapid, and sudden deaths have been reported. Severe toxicity may occur without preceding milder symptoms (see also 4.9 Overdose).

Immune system disorders:
Hypersensitivity reactions (see also Skin and subcutaneous tissue disorders).

Metabolism and nutrition disorders:
Metabolic disturbances such as hypokalaemia, hypophosphataemia, and hyponatraemia may occur.

Psychiatric disorders:
Insomnia, anxiety. Higher doses may lead to maniacal behaviour, delirium and convulsions.

Nervous system disorders:
Headache, confusion, restlessness, hyperventilation, vertigo/dizziness, tremor.

Eye disorders:
Visual disturbances.

Cardiac disorders:
Palpitations, tachycardia, cardiac arrhythmias, hypotension.

Gastrointestinal disorders:
Nausea, vomiting, abdominal pain, diarrhoea, gastro-oesophageal reflux, gastrointestinal bleeding.

Skin and subcutaneous tissue disorders:
Rash, maculo-papular rash, erythema, pruritus, urticaria, exfoliative dermatitis.

General/Administration site reactions:
Higher doses may result in hyperthermia and extreme thirst. Intramuscular injections are painful, the pain lasting several hours.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.11 Overdose

Aminophylline has a narrow therapeutic index. Theophylline toxicity is most likely to occur when serum concentrations exceed 20 micrograms/ml and becomes progressively more severe at higher serum concentrations.

Fatalities in adults have occurred during IV Aminophylline administration in large doses in patients with renal, hepatic or cardiovascular complications or where the injection has been given rapidly.

Symptoms
Tachycardia, in the absence of hypoxia, fever or administration of sympathomimetic drugs, may be an indication of theophylline toxicity.

Gastro-intestinal symptoms:
Anorexia, nausea, vomiting, diarrhoea, and haematemesis.

Neurological symptoms:
Restlessness, insomnia, irritability, headache, agitation, hallucinations, extreme thirst, slight fever, dilated pupils, and tinnitus. Seizures may occur even without preceding symptoms of toxicity and often result in death. Coma may develop in very severe cases.

Cardiovascular symptoms:
Palpitations, arrhythmias, hypotension, supraventricular and ventricular arrhythmias may occur.

Metabolic symptoms:
Hypokalaemia can develop rapidly and may be severe. Hyperglycaemia, albuminuria, hyperthermia, hypomagnesaemia, hypophosphataemia, hypercalcaemia, respiratory alkalosis and metabolic acidosis may also occur. Rhabdomyolysis may also occur.

Treatment
Treatment of overdosage is supportive and symptomatic. Serum theophylline and potassium levels should be monitored. Repeated oral administration of activated charcoal enhances the elimination of theophylline from the body even after intravenous administration. Aggressive antiemetic therapy may be required to allow administration and retention of activated charcoal.

Seizures may be treated with IV diazepam 0.1-0.3mg/kg up to 10mg. Restoration of fluid and electrolytes balance is necessary. Hypokalaemia should be corrected by intravenous infusion of potassium chloride. Sedation with diazepam may be required in agitated patients.

Propranolol may be administered intravenously to reverse extreme tachycardia, hypokalaemia and hyperglycaemia provided the patient does not suffer from asthma.

In general, theophylline is metabolised rapidly and haemodialysis is not warranted. In patients with congestive heart failure or liver disease, haemodialysis may increase theophylline clearance by as much as 2-fold.

Charcoal haemoperfusion should be considered if:

- Ileus/ intestinal obstruction prevents administration of multiple dose activated charcoal.

- Plasma theophylline concentration > 80mg/L (acute) or > 60mg/L (chronic).

In infants under 6 months of age or the elderly, charcoal haemoperfusion should be considered at theophylline concentrations >40 mg/L. Clinical features rather than theophylline concentration are the best guide for treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Xanthines, ATC code: R03DA05

Mechanism of Action:
Aminophylline is a soluble derivative of theophylline and is given for its theophylline activity. Aminophylline relaxes smooth muscle and relieves bronchial spasm. It stimulates the myocardium and reduces venous pressure in congestive heart failure, leading to a marked increase in cardiac output. It has stimulant effect on respiration, and also a diuretic action of short duration.

5.4 Pharmacokinetic properties

Distribution:
Theophylline is approximately 60% bound to plasma proteins but binding is decreased to about 40% in neonates and in adults with hepatic disease. The drug is widely distributed and it crosses the placenta and passes into breast milk.

Biotransformation and Elimination:
Theophylline is metabolised in the liver and the metabolites are excreted in the urine. In adults, about 10% of a dose of theophylline is excreted unchanged in the urine. There is considerable inter-individual variation in the rate of hepatic metabolism of theophylline, resulting in large variations in clearance, serum concentrations and half-lives. Cigarette smoking increases theophylline clearance and shortens its serum half-life.

5.3. Pre-clinical Safety Data

No further information other than that which is included in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Ethylenediamine Ph. Eur.
Water For Injections Ph. Eur.

6.2. Incompatibilities

Aminophylline injection is not stable in solutions having a pH of substantially less than 8, however, the drug appears to be relatively stable in large volume parenteral solutions over a wide pH range (3.5-8.6) if Aminophylline concentrations do now exceed 40mg per ml. The activity of alkali-sensitive drugs will be reduced by Aminophylline, these drugs should not be added to IV fluids containing Aminophylline.

6.3. Shelf-Life

36 months.

6.4 Special precautions for storage

Do not store above 25°C

6.5. Nature and Contents of Container

10ml clear glass ampoules, packed in cardboard cartons to contain 10 ampoules

6.7 Special precautions for disposal and other handling

Use as directed by a physician.

7. MARKETING AUTHORISATION HOLDER

hameln pharma ltd
Nexus, Gloucester Business Park
Gloucester, GL3 4AG

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 01502/0009R

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/04/2008

10 DATE OF REVISION OF THE TEXT

16/08/2022