WHO-PQ recommended clinical and preclinical information for the health care provider

This information reflects the recommendations of current WHO guidelines and the scope of WHO's prequalification programme.

1. TYPE OF THE MEDICINAL PRODUCT

[AP002 trade name]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Caffeine citrate10mg/ml
For product-specific information, see WHOPAR part 4.

3. PHARMACEUTICAL FORM

solution for injection
For product-specific information, see WHOPAR part 4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[AP002 trade name] is indicated for:

- treating apnoea in preterm neonates
- preventing apnoea after extubation of preterm neonates of gestational age up to 37 weeks
- preventing apnoea in preterm neonates of gestational age less than 34 weeks.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

[AP002 trade name] is given by intravenous infusion; administration can be switched to the oral route if appropriate.

Treatment of apnoea in preterm neonates

Initial dose: caffeine citrate 20 mg/kg by intravenous infusion over 30 minutes as a single dose then after 24 hours, caffeine citrate 5 mg/kg daily by intravenous infusion over 10 minutes for 6 weeks or until there is adequate clinical response.

Extubation of preterm neonates born up to 37 weeks after gestation

Initial dose: caffeine citrate 20 mg/kg by intravenous infusion over 30 minutes as a single dose then after 24 hours, caffeine citrate 5 mg/kg daily by intravenous infusion over 10 minutes for 6 days.

Prevention of apnoea in preterm neonates born before 34 weeks' gestation

Initial dose: caffeine citrate 20 mg/kg by intravenous infusion over 30 minutes as a single dose then after 24 hours, caffeine citrate 5 mg/kg daily by intravenous infusion over 10 minutes for 6 weeks or according to clinical needs.

Note

Doses are expressed as **caffeine citrate**; 2 mg of caffeine citrate is equivalent to 1 mg caffeine (base).

Plasma caffeine concentration

Plasma caffeine concentration monitoring is rarely necessary. It may be used to adjust the daily dose when higher dose is needed or if toxicity is suspected. Caffeine concentrations associated with clinical benefit range between 8 and 30 mg/litre; toxicity is unlikely with plasma concentration below 50 mg/litre.

Consumption of large amounts of caffeine by the mother before delivery may mean that the neonate already has circulating caffeine before [AP002 trade name] is given. Previous treatment of the neonate with theophylline can also contribute to plasma caffeine concentration.

Renal impairment

Daily doses of caffeine citrate may need to be reduced in renal impairment to prevent accumulation. The dose can be adjusted according to clinical response and, if available, measurement of caffeine concentration in blood.

Hepatic impairment

Hepatic function does not affect the clearance of caffeine in very premature neonates but in an older infant, hepatic disease may impair caffeine metabolism and the dose of caffeine may need to be reduced.

Method of administration

[AP002 trade name] is given by **slow** intravenous infusion through a metered infusion device (such as a syringe pump). Alternatively, it can be diluted with sterile infusions of glucose 50 mg/mL (5%) *or* sodium chloride 9 mg/mL (0.9%) *or* calcium gluconate 100 mg/mL (10%).

Rapid intravenous injection should be avoided because it may cause sudden changes in blood pressure. [AP002 trade name] should **not** be injected by any other route.

[AP002 trade name] should be given regularly every 24 hours. Administration can be switched to the oral route if appropriate.

4.3 Contraindications

Hypersensitivity to caffeine citrate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Inadequate response

If apnoea in the premature infant does not respond to adequate doses of caffeine citrate, other causes of apnoea should be considered.

Seizure disorders

Caffeine citrate must be used with extreme caution in neonates with seizure disorders since seizures have occurred with caffeine overdose.

Cardiovascular disorders

Caffeine citrate should be used cautiously in neonates with cardiovascular disease or in those whose cardiotocograph before birth showed unusual rhythm disturbances. Caffeine citrate may cause sinus tachycardia.

Renal and hepatic impairment

The frequency of adverse effects may be increased in very premature neonates with renal or hepatic impairment. Care is required with the dose in these neonates to avoid toxicity.

Gastro-intestinal disorders

Pre-term neonates receiving caffeine citrate should be monitored for the development of necrotising enterocolitis although a causal relationship between caffeine citrate and necrotising enterocolitis has not been

established. Reduced gastric acid secretion may promote bacterial overgrowth and increase the risk of necrotising enterocolitis.

Caffeine citrate should be used with caution in neonates suffering from gastro-oesophageal reflux since caffeine citrate may exacerbate the condition.

Metabolic changes and diuresis

Caffeine citrate increases metabolic rate, which may result in higher energy and nutritional requirements.

The diuretic effect of caffeine citrate may necessitate correction of fluid and electrolyte disturbances.

Excipients

Information on excipients with a recognised clinical effect can be found in the product information as approved by the reference authority, stated in WHOPAR part 1.

4.5 Interaction with other medicinal products and other forms of interaction

Caffeine metabolism is limited in preterm neonates because of their immature hepatic enzyme systems. As these systems mature, caffeine is mainly metabolised by CYP1A2, and substrates, inhibitors and inducers of CYP1A2 can affect caffeine metabolism in older infants.

Caffeine is a methylxanthine and concurrent use of other methylxanthines such as aminophylline and theophylline should be avoided. Aminophylline or theophylline are metabolised to caffeine. When switching treatment to [AP002 trade name] it is important to consider that caffeine may be present in the blood from previous treatment.

Medicines that suppress gastric acid secretion (such as H2-receptor blockers and proton-pump inhibitors) may allowing bacterial overgrowth. Therefore, co-administration of these medicines with caffeine citrate may increase the risk of necrotising enterocolitis.

Concurrent use of caffeine and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous system. If used concurrently, cardiac rhythm and blood pressure must be carefully monitored.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Caffeine readily crosses the placenta into the fetal circulation. Consumption of large amounts of caffeine before delivery may mean that the neonate already has circulating caffeine before [AP002 trade name] is given.

Breast-feeding

Breast-feeding mothers of neonates treated with [AP002 trade name] should not ingest caffeine-containing drinks, foods or medicines, since caffeine passes into breast milk.

Fertility

Treatment of the neonate with caffeine citrate is not likely to have any effect on fertility. The effect of caffeine in animal reproduction studies is not relevant to caffeine citrate treatment of preterm neonates.

4.7 Effects on ability to drive and use machines

The effect of [AP002 trade name] on the performance of skilled tasks is not relevant to neonates.

4.8 Undesirable effects

Summary of the safety profile

The adverse effects of caffeine citrate, predicted from its pharmacology and toxicology, include central nervous system (CNS) stimulation such as convulsion, irritability, restlessness and jitteriness, cardiac effects

such as tachycardia, arrhythmia, hypertension and increased stroke volume, metabolic effects such as hyperglycaemia. These effects are dose related.

Tabulated list of adverse reactions

Adverse reactions of [AP002 trade name] are listed below by body system or organ. Frequencies are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10) uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Infections and infestations	
Not known	sepsis
Immune system disorders	
Rare	hypersensitivity reaction
Metabolism and nutrition disorders	
Common	hyperglycaemia
Not known	hypoglycaemia, failure to thrive, feeding intolerance
Nervous system disorders	
Uncommon	convulsion
Not known	irritability, jitteriness, restlessness, brain injury
Ear and labyrinth disorders	
Not known	deafness
Cardiac disorders	
Common	tachycardia
Uncommon	arrhythmia
Not known	increased left ventricular output and increased stroke volume
Gastrointestinal disorders	
Not known	regurgitation, increased gastric aspirate, necrotising enterocolitis
General disorders and administration-site conditions	
Common	infusion-site phlebitis, infusion-site inflammation
Investigations	
Not known	increased urine output, raised urine sodium and calcium, decreased haemoglobin, decreased thyroxine

Description of selected adverse reactions

Use of methylxanthines (such as caffeine) may be associated with the development of necrotising enterocolitis, a condition that can lead to significant morbidity and mortality. However, a causal relationship has not been established between the use of caffeine citrate and necrotising enterocolitis. Preterm neonates should be monitored for the development of necrotising enterocolitis.

Brain injury, convulsion and deafness occurred in a clinical study involving preterm neonates but these effects were more frequent in neonates receiving placebo.

Caffeine may suppress erythropoietin synthesis and hence reduce haemoglobin concentration with prolonged treatment.

Transient fall in thyroxine (T4) has been reported in neonates at the start of treatment but thyroxine decrease is not sustained with continuing treatment.

There is no evidence that treatment of preterm neonates causes long-term effect on neurodevelopmental outcome, failure to thrive or on the cardiovascular, gastrointestinal or endocrine systems. Caffeine is unlikely to aggravate cerebral hypoxia or exacerbate any resulting damage.

Adverse reactions of caffeine citrate may be more frequent in premature neonates with renal or hepatic impairment. Such reactions mostly include cardiac disorder (tachycardia and one report of arrhythmia).

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Plasma caffeine levels following overdose have ranged between 50 and 350 mg/litre.

Signs and symptoms of overdose

Signs and symptoms of caffeine overdosage reported in neonates and premature neonates include jitteriness, tachycardia, tachypnoea, opisthotonos, rigidity and tonic-clonic movements, hypokalaemia, fine tremor of the extremities, restlessness, gastric irritation, gastro-intestinal haemorrhage, increased white blood cell count, and non-purposeful jaw and lip movements.

Effects from gross overdose include fever, agitation, hyperexcitability, hypertonia, gastric residues, distended abdomen, metabolic acidosis, hyperglycaemia and elevated urea levels. No deaths from caffeine overdose have been reported in preterm neonates.

One case of caffeine overdose was complicated by intraventricular haemorrhage and long-term neurological sequelae. In another case, circulation was compromised and the neonate developed vomiting and seizures.

Management

Caffeine overdose in preterm neonates is managed by supportive measures. Plasma potassium and glucose concentrations should be monitored and hypokalaemia and hyperglycaemia corrected. Previous cases reported resolved satisfactorily.

Caffeine concentration in the blood may be monitored during management of an overdose.

Convulsions may be treated with intravenous administration of an anticonvulsant (such as phenobarbital, phenytoin or levetiracetam).

In severe overdose, exchange transfusion should be considered. In one case, each transfusion reduced plasma caffeine concentration by 40mg/litre.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics xanthine derivatives

ATC code: N06BC01

Mechanism of action

Caffeine is a methylxanthine and is related to theophylline and theobromine.

As a CNS stimulant, caffeine increases inspiratory drive and regularises breathing pattern. At therapeutic plasma concentration, caffeine is an antagonist at both A_1 and A_{2A} adenosine receptors; this blockade is thought to increase respiratory drive.

Clinical efficacy and safety

Evidence on the benefit of caffeine citrate in preterm neonates comes from a 2023 Cochrane review of 18 clinical studies involving a total of 2705 neonates. Treatment with caffeine citrate reduces chronic lung disease and may reduce the risk of death and major neurodevelopmental disability at 18 to 24 months.

Efficacy for treatment of apnoea

Results are shown below of 6 clinical studies involving 959 preterm neonates (gestational age less than 37 weeks) treated for apnoea with a methylxanthine (including caffeine). There was evidence of moderate benefits and no evidence of harm.

Outcome	**Study population**	**Relative risk; confidence interval**
Decreased apnoeic episodes	1 study; 43 preterm neonates	RR 0.70; 95% CI 0.30 to 1.62
Decreased use of mechanical ventilation	5 studies; 192 preterm neonates	RR 0.34; 95% CI 0.12 to 0.97
Decreased bronchopulmonary dysplasia (need for supplemental oxygen) at 36 weeks gestational age	1 study; 805 preterm neonates	RR 0.72; 95% CI 0.58 to 0.89
Decreased death or major neurodevelopmental disability (up to 5 years' follow up)	1 study; 767 preterm neonates	RR 0.85; 95% CI 0.71 to 1.01

Efficacy after extubation

Results are shown below of 7 clinical studies involving 870 preterm neonates (gestational age less than 34 weeks) treated with a methylxanthine (including caffeine) after extubation to prevent apnoea. There was evidence of moderate benefits and no evidence of harm.

Outcome	**Study population**	**Relative risk; confidence interval**
Decreased failed extubation (i.e. need for re-intubation)	6 studies; 197 preterm neonates	RR 0.48; 95% CI 0.32 to 0.71
Decreased bronchopulmonary dysplasia (need for supplemental oxygen) at 36 weeks gestational age	2 studies; 704 preterm neonates	RR 0.81; 95% CI 0.70 to 0.92
Decreased death or major neurodevelopmental disability (up to 5 years' follow up)	1 study; 676 preterm neonates	RR 0.85; 95% CI 0.73 to 0.99

Efficacy for prevention of apnoea

Results are shown below of 7 clinical studies involved 706 preterm neonates treated with a methylxanthine (including caffeine) for the prevention of apnoea. There was evidence of small or moderate benefit of decreasing bronchopulmonary dysplasia and apnoeic episodes but little or no effect on reducing death. The evidence of harm was uncertain, with low-certainty evidence of an *increase* in the use of mechanical ventilation.

Outcome	**Study population**	**Relative risk; confidence interval**
Decreased apnoeic episodes by hospital discharge	2 studies; 104 preterm neonates	RR 0.19; 95% CI 0.09 to 0.41
Decreased use of mechanical ventilation	4 studies; 208 preterm neonates	RR 1.33; 95% CI 0.48 to 3.72

Outcome	Study population	Relative risk; confidence interval
Decreased bronchopulmonary dysplasia (need for supplemental oxygen) at 36 weeks gestational age	3 studies; 541 preterm neonates	RR 0.78; 95% CI 0.63 to 0.97
Decreased death or major neurodevelopmental disability (up to 5 years' follow up)	1 study; 423 preterm neonates	RR 1.00; 95% CI 0.80 to 1.24
Decreased death	3 studies; 129 preterm neonates	RR 2.19; 95% CI 0.85 to 5.68

General safety concerns

Caffeine increases metabolic rate, heart rate, cardiac contractility and output. It also increases blood flow to the kidneys, and prevents sodium and chloride reabsorption at the proximal tubules, which can lead to mild diuresis.

Adenosine is a vasodilator and therefore caffeine, as its antagonist, can cause vasoconstriction. Hence it is a vasoconstrictor in the cerebral and splanchnic circulations. Elsewhere, it has a vasodilator effect due to an effect on vascular smooth muscle.

The stimulant effect may affect sleep patterns.

5.2 Pharmacokinetic properties

Further information on pharmacokinetic properties is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

General	The route of administration does affect the pharmacokinetics of caffeine citrate.
Absorption	Caffeine citrate is rapidly and completely absorbed after oral administration; bioavailability is the same whether caffeine citrate is given orally or intravenously. After oral administration of caffeine **base** 10 mg/kg to preterm neonates, C_{max} ranged from 6 to 10 mg/L and t_{max} ranged from 0.5 to 2 hours.
Food effect	The extent of absorption is not affected by formula feeds, but t_{max} may be prolonged.
Distribution	
Volume of distribution (mean)	0.8–0.9 L/kg
Plasma protein binding	Plasma protein binding data are not available for neonates infants or infants. In adults, mean plasma protein binding in vitro is reported to be about 36%.
Tissue distribution	Caffeine distributes rapidly, including into the brain. It does not accumulate in tissue. In preterm neonates, caffeine levels in the cerebro-spinal fluid are similar to those in plasma. Caffeine readily crosses the placenta into the fetal circulation and is present in breast milk.
Metabolism	
	Metabolism is limited in preterm neonates because hepatic enzyme systems are immature and most of the active substance is eliminated in urine. In preterm neonates, caffeine mainly undergoes N7-demethylation through CYP1A2. There is almost no first-pass metabolism. The rate of caffeine metabolism in female neonates may be higher than in males.
Active metabolite(s)	3–8% of the dose may be converted to theophylline
Elimination	
Elimination half life	In neonates, caffeine is cleared almost entirely by renal excretion. In infants, mean $t_{½}$ and the amount of caffeine excreted unchanged in the urine are inversely related to gestational/postmenstrual age. In neonates, the $t_{½}$ is about 3–4 days and by 9 months of age, the metabolism of caffeine approximates that in adults ($t_{½}$ = 5 hours).
Mean systemic clearance (Cl/F)	2–17 mL/kg/hour, depending on gestational age
% of dose excreted in urine	In newborn infants, the amount of caffeine excreted unchanged is about 86% (within 6 days). By 9 months of age, the amount is about 1%.
Drug interactions	
Metabolising enzymes	Mainly CYP1A2; partly xanthine oxidase

Pharmacokinetics of caffeine citrate in neonates

Pharmacokinetics in special populations

Studies are not available on the pharmacokinetics of caffeine in neonates with hepatic or renal insufficiency.

In the presence of significant renal impairment, considering the increased potential for accumulation, a reduced daily maintenance dose of caffeine is required and the dose should be guided by blood caffeine measurements. In premature neonates with cholestatic hepatitis, prolonged caffeine elimination half-life and plasma levels raised above the normal limit of variation have been found, calling for particular caution in the dosage of these patients.

5.3 Preclinical safety data

There is no relevant preclinical data on the use of caffeine citrate in premature neonates.

6. PHARMACEUTICAL PARTICULARS

Information on the pharmaceutical particulars is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

7. SUPPLIER

Information on the supplier is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

The WHO reference number is shown in WHOPAR part 1

9. DATE OF PREQUALIFICATION

The date of prequalification can be found in WHOPAR part 1.

10. DATE OF REVISION OF THE TEXT

January 2026

References

WHO recommendations for care of the preterm or low birth weight infant. Geneva: World Health Organization; 2022 (https://iris.who.int/server/api/core/bitstreams/707c8feb-e4e4-4e5c-b029-b78202c67cc7/content, accessed 22 November 2025).

Caffeine Citrate 10mg/ml Oral Solution (Macarthys Laboratories Limited): summary of product characteristics. MHRA; 4 September 2018 (available at: https://products.mhra.gov.uk, accessed 22 November 2025)

Caffeine Citrate 10mg/ml Solution for Injection (Macarthys Laboratories Limited): summary of product characteristics. MHRA; 31 March 2020 (available at: https://products.mhra.gov.uk, accessed 22 November 2025)

Peyona 20 mg/mL solution for infusion; summary of product characteristics. EMA; 18 September 2024 (https://www.ema.europa.eu/en/documents/product-information/peyona-epar-product-information_en.pdf, accessed 9 December 2025)

Section 4.9

Pressler RM, Abend NS, Auvin S, et al. Treatment of seizures in the neonate: Guidelines and consensus-based recommendations—Special report from the ILAE Task Force on Neonatal Seizures. Epilepsia. 2023;64:2550–2570. doi: 10.1111/epi.17745.

Section 5.1

Marques KA, Bruschettini M, Roehr CC, et al. Methylxanthine for the prevention and treatment of apnea in preterm infants. Cochrane Database Syst Rev. 2023;10:CD013830. doi: 10.1002/14651858.CD013830.pub2.

Section 5.2

Abdel-Hady H, Nasef N, Shabaan AE, Nour I. Caffeine therapy in preterm infants. World J Clin Pediatr. 2015;4:81–93. doi: 10.5409/wjcp.v4.i4.81.