1. NAME OF THE MEDICINAL PRODUCT

JAWAMOX NEONATAL DROPS

(Amoxicillin for oral suspension 100 mg/ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Amoxicillin Trihydrate BP

Eq. To anhydrous Amoxicillin 100 mg

3. PHARMACEUTICAL FORM

Dosage Form: Powder for oral Suspension

A white powder filled in a glass bottle which turns yellow on reconstitution, packed in a 20 ml Amber glass bottle with a 10mls sterilized water for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin is indicated for the treatment of the following bacterial infections caused by amoxicillin-sensitive gram-positive and gram-negative pathogens:

• Infections of the upper respiratory tract, including infections of the ears, nose and throat: Acute otitis media, acute sinusitis and bacterial pharyngitis.

• Infections of the lower respiratory tract: Acute exacerbation of chronic bronchitis, community-acquired pneumonia.

• Infections of the lower urinary tract: Cystitis.

• Prophylaxis of endocarditis in patients at risk i.e. surgery in the oral cavity or upper airways.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

4.2 Posology and method of administration

The dosage of amoxicillin is dependent on age, bodyweight and renal function of the patient, on the seriousness and localisation of the infection and on the expected or proved causative agent.

Standard dosage

Adult and adolescents (> 40 kg body weight):

The usual dosage covers a range from 750 mg to 3g amoxicillin daily in divided doses. In some areas 1500 mg amoxicillin daily in divided doses are recommended as the upper usual dose.

Special dosage recommendation

Acute exacerbation of chronic bronchitis in adults: 2 x 1 g per day

Children's dosage (under 40 kg)

The daily dosage for children is 40 - 90 mg/kg/day in two to three divided doses* (not exceeding 3 g/day) depending on the indication, the severity of the disease and the susceptibility of the pathogen (see special dosage recommendations below and sections 4.4, 5.1 and 5.2).

*PK/PD data indicate that dosing three times daily is associated with enhanced efficacy, thus twice daily dosing is only recommended when the dose is in the upper range.

Children weighing more than 40 kg should be given the usual adult dosage.

Special dosage recommendation

Tonsillitis: 50 mg/kg/day in two divided doses.

Acute otitis media: In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations.

Dosage for the prevention of endocarditis

For the prevention of endocarditis, in patients not having general anaesthetic, 3 g amoxicillin are given orally in the hour preceding the surgical procedure, followed by (6 hours later) a further 3 g dose, if considered necessary.

For children: 50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure..

For further details and description of patients at risk local official guidelines for the prevention of endocarditis should be consulted.

Dosage in patients with impaired renal function:

The dose should be reduced in patients with severe renal function impairment. In patients with a renal clearance of less than 30 ml/min an increase in the dosage interval and a reduction in the total daily dose is recommended.

Adults (including older patients):

Creatinine clearance ml/min	Dose	Interval between administration
> 30	No adjustment necessary.	
10 – 30	500 mg	12 h
< 10	500 mg	24 h

In case of hemodialysis: 500 mg should be administered at the end of the procedure.

Renal impairment in children under 40 kg:

Creatinine clearance ml/min	Dose	Interval between administration
> 30	Usual dose	No adjustment necessary.
10 – 30	Usual dose	12 h (corresponding to 2/3 of the dose)
< 10	Usual dose	24 h (corresponding to 1/3 of the dose)

Dosage in patients with impaired hepatic function

No dose reduction is necessary as long as the renal function is not impaired.

Duration of therapy:

In general the therapy should be continued for 2 to 3 days following the disappearance of symptoms. In β-haemolytic streptococcal infections the duration of therapy should be 6-10 days in order to achieve eradication of the organism.

Method of administration:

The preparation is administered orally with a measuring spoon. The measuring spoon is included in the package. The ready-for-use suspension should be taken with a glass of water.

The absorption of amoxicillin is not reduced by food intake.

Administration to babies: The prescribed dosage is administered undiluted to the baby; milk or tea should be given afterwards**.**

4.3 Contraindications:

Amoxicillin is contraindicated in patients with:

• Hypersensitivity to penicillin; a cross-allergy to other beta-lactams such as cephalosporins should be taken into account.

4.4 Special warnings and precautions for use:

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins and cephalosporins. The possibility of cross-hypersensitivity (10 % - 15 %) with cephalosporins should be taken into account.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of hypersensitivity to beta-lactam antibiotics.

In patients with renal function impairment the excretion of amoxicillin will be delayed and, depending on the degree of the impairment, it may be necessary to reduce the total daily dosage (see section 4.2).

Precaution should be taken in premature children and during neonatal period: renal, hepatic and haematological functions should be monitored.

The prolonged use of amoxicillin may occasionally result in an overgrowth of non- susceptible bacteria or yeasts. Patients should therefore carefully be watched for superinfections.

The occurrence of anaphylactic shock and other severe allergic reactions is rare following the oral administration of amoxicillin. However, if such reactions occur, appropriate emergency treatment measures must be taken.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.

At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria.

Amoxicillin should not be used for the treatment of bacterial infections in patients with viral infections, acute lymphatic leukaemia, or infectious mononucleosis as erythematous (morbilliform) rashes have been associated with glandular fever in patients receiving amoxicillin.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

As with other beta-lactams, the blood formula should be checked regularly during high-dose therapy.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

High dose therapy with beta-lactams for patients with renal insufficiency or seizures history, treated epilepsy and meningeal affection, could exceptionally lead to seizures.

The occurrence of a generalized erythema with fever and pustules at the beginning of treatment should make suspect a generalized acute exanthematic pustulosis; this necessitates the interruption of therapy and contraindicated any further administration of amoxicillin.

All Amoxicillin powders for oral suspension contain aspartame (E951) and should be used with care in patients with phenylketonuria. In homozygotic patients with phenylketonuria, the amount of phenylalanine that is supplied by aspartame must be included in the calculation for the dietary regulations.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Allopurinol

Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions and is therefore not advised.

Digoxin

An increase in the absorption of digoxin is possible on concurrent administration with amoxicillin. A dose adjustment of digoxin may be necessary.

Anticoagulants

Concomitant administration of amoxicillin and anticoagulants from the coumarin class, may prolong the bleeding time. A dose adjustment of anticoagulants may be necessary. A large number of cases showing an increase of oral anticoagulant activity has been reported in patients receiving antibiotics. The infectious and inflammatory context, age and the general status of the patient appear as risk factors. In these circumstances, it is difficult to know the part of the responsibility between the infectious disease and its treatment in the occurrence of INR disorders. However, some classes of antibiotics are more involved, notably fluoroquinolones, macrolides, cyclines, cotrimoxazole and some cephalosporins

Methotrexate

Interaction between amoxicillin and methotrexate leading to methotrexate toxicity has been reported. Serum methotrexate levels should be closely monitored in patients who receive amoxicillin and methotrexate simultaneously. Amoxicillin decreases the renal clearance of methotrexate, probably by competition at the common tubular secretion system.

Caution is recommended when amoxicillin is given concomitantly with:

Oral hormonal contraceptives

Administration of amoxicillin can transiently decrease the plasma level of estrogens and progesterone, and may reduce the efficacy of oral contraceptives. It is therefore recommended to take supplemental non-hormonal contraceptive measures.

Other forms of interactions:

− Forced diuresis leads to a reduction in blood concentrations by increased elimination of amoxicillin.

− It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

− Amoxicillin may decrease the amount of urinary estriol in pregnant women.

− At high concentrations, amoxicillin may diminish the results of serum glycemia levels.

− Amoxicillin may interfere with protein testing when colormetric methods are used.

4.6 Pregnancy and lactation

Pregnancy

Amoxicillin passes the placenta and foetal plasma concentrations are approximately 25-30% of the maternal plasma concentrations.

Data on a limited number of exposed pregnancies indicate no adverse effects of amoxicillin on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

Breast-feeding

Amoxicillin is excreted into breast milk (approx. 10% of the corresponding serum concentration). So far no detrimental effects for the breast-fed infant have been reported after taking amoxicillin. Amoxicillin can be used during breast-feeding.

However, breast-feeding must be stopped if gastrointestinal disorders (diarrhoea, candidosis or skin rash) occur in the new born.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions),which may influence the ability to drive and use machines.

4.8 Undesirable effects

In this section undesirable effects are defined as follows:

Very common	*≥1/10*
Common	*≥1/100 to <1/10*
Uncommon	*≥1/1,000 to <1/100*
Rare	*≥1/10,000 to < 1/1,000*
Very rare	*<1/10,000,*

Not known (cannot be estimated from the available data)

Infections and infestations

Uncommon

Superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis after prolonged and repeated use of amoxicillin.

Blood and the lymphatic system disorders

Rare

Eosinophilia and haemolytic anaemia.

Very rare

Leucopenia, neutropenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia, myelosuppression, agranulocytosis, prolongation of bleeding time, and prolongation of prothrombin time. All were reversible on discontinuation of therapy.

Immune system disorders

Rare

Laryngeal oedema, serum sickness, allergic vasculitis, anaphylaxis and anaphylactic shock.

Nervous system disorders

Rare

CNS effects including hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function, epilepsy, meningitis or in those receiving high doses.

Gastrointestinal disorders:

Common

Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side effects can generally be reduced by taking amoxicillin during meals.

Rare

Superficial discoloration of the teeth (especially with the suspension). Usually the discoloration can be removed by teeth brushing.

Very rare

If severe and persistent diarrhoea occurs, the very rare possibility of pseudomembranous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.

Development of a black tongue.

Hepato-biliary disorders:

Uncommon

Moderate and transient increase of liver enzymes.

Rare

Hepatitis and cholestatic jaundice.

Skin and subcutaneous tissue disorders:

Common

Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5 - 11 days after start of therapy. Immediate appearance of urticariaindicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.

Rare (see also section 4.4).

Angioneurotic oedema (Quincke's oedema), Erythema multiforme exsudativum, acute generalized pustulosis, Lyell's syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis.

Renal disorders

Rare

Acute interstitial nephritis. Crystalluria.

General disorders and administration site conditions

Rare

Drug fever.

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 (www.mhra.gov.uk/yellowcard).

4.9 Overdose

Symptoms of overdose:

Amoxicillin is not generally associated with acute toxic effects, even when accidentally consumed in high doses. Overdosage can lead to symptoms such as gastrointestinal renal and neuro-psychic disturbances and fluid and electrolyte imbalance. In patients with severely impaired renal function, large overdoses can result in signs of renal toxicity; crystalluria is possible.

Management of overdose:

There is no specific antidote for an overdose of amoxicillin.

Treatment consists primarily of administration of activated charcoal (a gastric lavage is usually not necessary), or symptomatic measures. Particular attention should be paid to the water and electrolyte balance of the patients.

Amoxicillin can be eliminated via haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC-Code: J01CA04

Pharmacotherapeutic group: Beta-lactam antibacterials, Penicillins with extended spectrum.

Mode of action

Amoxicillin is an aminobenzyl penicillin that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

PK/PD relationship

For amoxicillin, time above MIC (T>MIC) is the key pharmacodynamic parameter in predicting a successful clinical and bacteriological outcome.

Mechanism of resistance

Bacteria may be resistant to amoxicillin due to production of beta-lactamases which hydrolyse aminopenicillins, due to alteration in penicillin-binding proteins, due to impermeability to the drug, or due to drug efflux pumps. One or more of these mechanisms

may co-exist in the same organism, leading to a variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

***Breakpoints* (EUCAST)**

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae	≤ 1	-	> 1
Moraxella catharrhalis	≤ 1	-	> 1
Enterococcus	≤ 4	8	> 8
Streptococcus A, B, C, G[1]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[2]	≤ 0.5	1-2	> 2
Enterobacteriaceae[3]	-	-	> 8
Gram-negative anaerobes	≤ 0.5	-	> 2
Gram-positive Anaerobes	≤ 4	8	> 8
Non-species related breakpoints	≤ 2	4-8	> 8

[1] Breakpoint values in the table are based on Benzylpenicillin breakpoints.

[2] Breakpoint values in the table are based on ampicillin breakpoints.

[3] The resistant breakpoint of R>8 mg/L ensures that all isolates with resistance mechanisms are reported resistant.

Susceptibility:

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive
Corynebactierum diphteriae
Enterococcus faecalis [$]
Listeria monocytogenes
Streptococcus agalactiae
Streptococcus bovis

Streptococcus pyogenes *
Aerobic Gram-negative
Helicobacter pylori
Anaerobes
Peptostreptococci
Others
Borrelia
Species for which acquired resistance may be a problem
Aerobic Gram-positive
Corynebacterium spp
Enterococcus faecium $
Streptococcus pneumoniae * +
Streptococcus viridans
Aerobic Gram-negative
Escherichia coli +
Haemophilus influenzae *
Haemophilus para-influenzae *
Moraxella catarrhalis +
Proteus mirabilis
Anaerobes
Prevotella
Fusobacterium spp
Inherently resistant organisms
Aerobic Gram-positive
Staphylococcus aureus
Aerobic Gram-negative
Acinetobacter spp
Citrobacter spp
Enterobacter spp
Klebsiella spp
Legionella
Morganella morganii

Proteus vulgaris
Providencia spp
Pseudomonas spp
Serratia spp
Anaerobes
Bacteroides fragilis
Others
Chlamydia
Mycoplasma
Rickettsia

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

+ pathogens resistance prevalence is > 50%

$ Naturally intermediate species

5.2 Pharmacokinetic properties

Absorption:

The absolute bioavailability of amoxicillin depends on the dose and ranges between 75 and 90%. In the dose range between 250 mg and 1000 mg the bioavailability (parameters: AUC and Cmax) is linearly proportional to the dose. At higher doses the extent of absorption decreases. The absorption is not affected by concomitant food intake. Oral administration of a single dose of 500 mg amoxicillin results in plasma concentrations of 6 - 11 mg/l. After administration of a single dose of 3 g amoxicillin, the plasma concentrations reach 27 mg/l. Peak plasma concentrations are present about 1-2 hours after administration.

Distribution:

Protein binding for amoxicillin is approximately 17%. Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. In healthy meninges amoxicillin diffuses badly in liquor cerebrospinalis. Amoxicillin crossesthe placenta and a small percentage is excreted into the breast milk.

Biotransformation and elimination:

The main route of excretion of amoxicillin is the kidney. About 60-80% of an oral dose of amoxicillin are excreted in unchanged active form in the urine within 6 hours of administration, and a small fraction is excreted in the bile. Approximately 7 - 25% of the

administered dose is metabolised to inactive penicilloic acid. The serum half-life in patients with normal renal function is approximately 1 – 1,5 hour. In patients with end-stage renal failure the half-life ranges between 5 to 20 hours. The substance is haemodialysable.

Pediatric population

In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similarto the inulin clearance (GFR) in this population. Following oral administration, the absorptionpattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Aerosil 200
Citric Acid
Methyl Paraben
Propyl Paraben
Sodium Citrate
Sodium CMC (MVP)
Sugar Pharmagrade

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in cool and dry place, Temperature below 30^0C. Protect from Moisture.

6.5 Nature and contents of container

20 ml Amber glass Bottle and a 10mls sterilized water for injection

6.6 Special precautions for disposal <and other handling>

Do not use **JAWAMOX NEONATAL DROPs** after the expiry date stated on the carton and tube.
Medicines should not be disposed off via wastewater or household waste.
Ask your pharmacist how to dispose of medicines no longer required.These measures will help to protect the environment.

7. APPLICANT/MANUFACTURER

MARKETING AUTHORISATION HOLDER

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