1. NAME OF THE MEDICINAL PRODUCT

Broxil 250 mg, hard capsule 250 mg
Broxil 500 mg, hard capsule 500 mg
Broxil 125 mg/5 ml, powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Broxil 250 mg capsule contains 250 mg pheneticillin (as pheneticillin potassium).
Each Broxil 500 mg capsule contains 500 mg pheneticillin (as pheneticillin potassium).
Broxil 125 mg/5 ml oral suspension contains 25 mg pheneticillin (as pheneticillin potassium) per ml suspension after addition of water, see section 6.6.

Broxil suspension contains aspartame, sodium and sorbitol.
Broxil suspension contains less than 1 mmol sodium (23 mg) per 20 ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Broxil 250 mg and Broxil 500 mg: hard capsule

The capsules are off-white and black, with “Broxil” printed on one side and “250 mg” or “500 mg” respectively printed on the other side.

Broxil 125 mg/5 ml: powder for oral suspension

The powder is light pink and after reconstitution with water it is an oral suspension with a pleasant taste.

4. CLINICAL PARTICULARS

4.1Therapeutic indications

Non-severe to moderately severe infections caused by pheneticillin-sensitive microorganisms, in particular streptococci infections such as:

- upper respiratory infections like pharyngitis
- lower respiratory infections like pneumonia
- infections of the skin and soft tissue like impetigo or abscesses

Official local guidelines, such as national recommendations for the correct use and prescription of antimicrobial agents, must be followed.

4.2 Posology and method of administration

Posology
For non-severe infections in organs with good blood flow:

Adult population:
3 times daily 250 mg (every 8 hours).

Paediatric population:
Children up to the age of 2 years old an average of a quarter and children aged 2-10 years an average of half the dose for adults. The table below shows the posology for a 24-hour period.

	children aged 0-2 years	children aged 2-10 years	adults and children aged 10 years and up
capsules			3 x 1 capsule of 250 mg
oral suspension 125 mg/5 ml	3 x 2.5 ml	3 x 5 ml	3 x 10 ml

Special posology guidelines

- The doses listed above may be increased for moderately severe infections by doubling the amount of Broxil each time and increasing the number of doses per 24 hours to a maximum of 6 (every 4 hours). If a high or very high dose is advisable and there is no (longer a) need for parenteral administration, 1 capsule of 500 mg may be given 3 to 6 times every 24 hours.
- A 10-day course is recommended for eliminating throat infections with ß-haemolytic streptococci.
- The treatment for the prevention of acute rheumatoid polyarthritis is long-term administration of two doses per day: adults 2 x 250 mg and children 2 x 125 mg.

Elderly population
No data are available.

Renal impairment
Caution should be observed when using high doses of Broxil in patients with renal impairment.

Hepatic impairment
No data are available.

Method of administration

For oral use
Preferably on an empty stomach 1 hour before or 2 hours after a meal.

Capsules: take with water, tea or a sugary drink. Swallow the capsule whole.

Powder for oral suspension:

The powder must be reconstituted with water first, see section 6.6.
The measuring cup has markings for 5 ml to 15 ml; put the measuring cup down and fill it up to the line. Dispense the oral suspension into the mouth and then take a sip of another liquid, such as water or a sugary drink.
For doses below 5 ml the amount should be measured with a syringe. It is advisable to enclose a syringe and a syringe adaptor. Screw the adaptor onto the bottle and pull the suspension into the syringe. Have the patient take the suspension directly from the syringe.

4.3 Contraindications

Hypersensitivity to one or more forms of penicillin or to any of the excipients listed in section 6.1. A history of cross-sensitivity to cephalosporins.
Broxil suspension contains aspartame and is contraindicated in children with phenylketonuria (PKU) and pregnant women with phenylketonuria, if the daily aspartame consumption exceeds 45 mg aspartame (= 25 mg phenylalanine).

Patients with fructose intolerance should not use Broxil suspension because it contains sorbitol, see also section 4.4.

4.4 Special warnings and precautions for use

There is cross-sensitivity with other penicillins, cephalosporins and other beta-lactam antibiotics. Caution is advised in patients with a history of allergies, in particular to medicinal products. There is cross-resistance with other penicillins. Cross-resistance with cephalosporins is possible as well. Broxil is not stable against staphylococci- and gonococci-penicillinase and is not effective against Gram-negative rods.

Prolonged treatment with high doses

The kidneys, liver and haematological status should be monitored during prolonged treatment with high doses. Caution is advised when very high doses of penicillins are given, in particular in case of renal impairment because of the risk of neurotoxicity.

Neutropenia

Neutropenia has been reported in patients who received Broxil (see section 4.8). Signs of neutropenia include fever, rash and eosinophilia. Monitoring of the leukocyte count is recommended during prolonged treatment with high doses.

Superinfection

Treatment with penicillins, in particular in case of prolonged use, changes the normal bacterial flora, which may lead to a superinfection with penicillin-resistant organisms, including *Clostridium difficile* or *Candida* infections. If patients develop diarrhoea during or after the administration of an antibiotic, pseudomembranous colitis should be considered as a diagnosis. If antibiotic-related colitis occurs, Broxil should be stopped immediately, a physician should be consulted and appropriate treatment should be initiated. Medicinal products that inhibit intestinal peristalsis are contraindicated in that case.

Diagnostic tests

Like other penicillins, Broxil may affect a number of diagnostic tests, such as urine glucose tests with copper sulfate, direct antiglobulin (Coombs) tests and a number of urine and serum protein tests. Penicillins may affect tests that use bacteria, such as the Guthrie test which uses *Bacillus subtilis* organisms to detect phenylketonuria.

Potassium level

Caution should be observed when using high doses of Broxil in patients with renal impairment or cardiac disorders (see sections 4.5 and 4.8).

Warnings about the excipients

Broxil suspension contains aspartame (E951) and should be used with caution in patients with phenylketonuria. For homozygous patients with phenylketonuria, the amount of phenylalanine in aspartame should be taken into account in the dietary instructions.

Broxil suspension also contains sodium benzoate (E211) and sorbitol (E420) (see section 6.1). Broxil suspension contains approx. 25 grams sorbitol per 100 ml. Each 5 ml dose unit supplies approx. 1.3 grams sorbitol.

4.5 Interaction with other medicinal products and other forms of interaction

Bacteriostatic agents

Broxil should not be administered concomitantly with bacteriostatic agents.

Inhibition of tubular secretion caused by medicinal products

Probenecid, phenylbutazone, oxyphenbutazone and to a lesser extent acetylsalicylic acid, indomethacin and sulfinpyrazone, may inhibit the tubular secretion of pheneticillin and prolong the half-life of pheneticillin.

Anticoagulants

Like other broad-spectrum bactericides, pheneticillin may prolong the prothrombin time. Concomitant administration of antibiotics, including pheneticillin, with anticoagulants such as acenocoumarol or phenprocoumon may alter the effect of the anticoagulants. It may be necessary to adjust the dosage of the anticoagulant.

Other antibiotics

Pheneticillin may antagonise the effect of tetracyclines doxycycline, minocycline and tetracycline. Concomitant administration of these medicinal products should therefore be avoided.

Oral typhus vaccine

Concomitant administration of pheneticillin with the oral typhus vaccine may neutralise the effect of the vaccine in the stomach. This interaction has not been observed with parenteral administration.

Methotrexate

Considerably reduced clearance of intravenously administered methotrexate has been reported with various penicillins.

Potassium level

Caution should be observed when using high doses of pheneticillin in patients who receive other medicinal products with potassium or potassium-sparing diuretics (see sections 4.4 and 4.8).

Caution is advised in patients who receive high doses of Broxil or medicinal products with potassium or potassium-sparing diuretics.

4.6 Fertility, pregnancy and lactation

Fertility
No data are available.

Pregnancy
Based on the available data, taking Broxil as prescribed during pregnancy is not harmful to the foetus.

Breastfeeding
Broxil is allowed during the breastfeeding period. Except for the risk of sensitisation, there are no data that show negative effects on the infant.

4.7 Effects on ability to drive and use machines

There are no data on the effect of Broxil on the ability to drive and reaction time. An effect is not likely, however.

4.8. Undesirable effects

The following frequencies are used to indicate adverse reactions:
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)

Blood and lymphatic system disorders
Very rare: low white blood cell count
Not known: neutropenia (see section 4.4)

Immune system disorders:
Very rare: severe allergic symptoms including dyspnoea, swelling of the mouth, throat or larynx, shock
Not known anaphylactic reaction, anaphylactic shock, hypersensitivity reactions (dyspnoea, swelling of the mouth, throat or larynx)

Metabolism and nutrition disorders
Not known hyperkalaemia (see sections 4.4 and 4.8)

Gastrointestinal disorders
Not known: diarrhoea, nausea and vomiting, pseudomembranous colitis, painful mouth or tongue, black hairy tongue

Skin and subcutaneous tissue disorders
Not known: skin rash, typical type I allergic symptoms (such as urticaria and purpura)

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 national reporting system listed in Appendix V.*

4.9. Overdose

Overdose may lead to gastrointestinal disorders and disruption of the fluid and electrolyte balance. Treatment should be symptomatic by maintaining the fluid electrolyte balance. After an oral overdose, have the patient vomit, if possible, and drink water with activated charcoal and administer an osmotic laxative if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic category: beta-lactam-sensitive penicillins, ATC code: J01CE05

Mechanism of action

Broxil contains the gastric acid-stable penicillin derivative pheneticillin potassium. Pheneticillin is part of the penicillin group. Penicillins inhibit the synthesis of the cell wall by inhibiting the proteins involved in cell wall synthesis, the penicillin-binding proteins (PBPs).
Pheneticillin is a bactericidal narrow-spectrum penicillin, effective against Gram-positive rods and cocci and a few Gram-negative cocci. Pheneticillin is not effective against β-lactamase-producing microorganisms Pheneticillin is inactivated by β-lactamases of staphylococci and gonococci.

Relationship between PK/PD
There are no known data on the relationship between PK/PD.

Resistance mechanisms
Resistance to pheneticillin is a result of the production of β-lactamases and modified penicillin-binding proteins (PBPs).

Cross-resistance
Pheneticillin shows cross-resistance with other penicillins, combinations of β-lactam antibiotics/β-lactamase inhibitors and cephalosporins.

The MIC (minimum inhibitory concentration) breakpoints for pheneticillin are as published by CLSI (formerly NCCLS).

Organism	**Sensitivity breakpoints (mg/l)**		
	Sensitive (S)	**Intermediate (moderate in-vitro activity) (I)**	**Resistant (R)**
Enterobacteriaceae:	≤ 8 mg/l	16 mg/l	≥ 32 mg/l
Staphylococcus species -	≤ 0.25 mg/l	-	≥ 0.5 mg/l
Enterococcus species	≤ 8 mg/l	-	≥ 16 mg/l
Haemophilus species	≤ 1 mg/l	2 mg/l	≥ 4 mg/l
*Streptococcus species** (other than *S. pneumoniae)*	≤ 0.25 mg/l	0.5-4 mg/l	≥ 8 mg/l

* A pneumococci isolate which is sensitive to penicillin is assumed to be sensitive to pheneticillin.

The prevalence of resistance of the selected strains may vary in terms of geography and time, and local information about resistance is needed, in particular when treating serious infections. If necessary, expert advice may be obtained if the local prevalence of resistance is such that the usefulness of the medicinal product is doubtful for at least a few types of infections.

Normally sensitive species
Staphylococcus species that do not produce beta-lactamase *Enterococcus species* *Streptococcus species**
Species where acquired resistance may be a problem
Enterobacteriaceae *Staphylococcus species* *Enterococcus species* *Haemophilus species* *Streptococcus species**
Naturally resistant species
Beta-lactamase-producing microorganisms

* Other than *S. pneumoniae*. A pneumococci isolate which is sensitive to penicillin is assumed to be sensitive to pheneticillin.

5.2. Pharmacokinetic properties

Absorption
Elimination in urine, which is independent of the serum concentration or the pharmacokinetic model, is a measure of absorption. After oral administration on an empty stomach, this is 72.4 ± 17% of the administered dose.

The C_{max} after an oral dose of 250 mg is reached after about 1 hour and is approx. 4 mg/l. The absorption is negatively affected by the presence of food in the stomach. Doubling the dose results in virtual doubling of the serum concentrations.

Distribution
The serum protein binding is 82%. The distribution volume is 1.3 l/kg. Placental passage is good. Measured concentrations in umbilical blood ranged from 10% to 100% of the concentrations in the mother's blood. Concentrations in breast milk and liquor are not known.

Biotransformation
About 30% of an orally administered dose is found as a metabolite in the urine. The main metabolite of pheneticillin is penicilloic acid.

Elimination
The half-life (ß-phase) is approx. 0.77 hours. Over a period of 0-12 hours after administration, 49.8 ± 12.3% of an oral dose is eliminated in unchanged form with the urine and 22.2 ± 14.4% is found in the urine as penicilloic acid.

5.3. Preclinical safety data

No particulars.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Broxil 250 mg and Broxil 500 mg
Capsule content: magnesium stearate (E470B)
Capsule coating: gelatine, titanium dioxide (E171), black iron oxide (E172), yellow iron oxide (E172)
Ink imprint: shellac (E904), titanium dioxide (E171) and vegetable carbon (E153)

Broxil 125 mg/5 ml
aspartame (E951) (15 mg/5ml equivalent to 8.3 mg phenylalanine per 5 ml)
sodium chloride
anhydrous sodium citrate
disodium edetate
sodium benzoate (E211)
cochineal red A (E124)
sorbitol (E420)
flavourings: banana, passion fruit, chocolate, peppermint

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Broxil 250 mg and Broxil 500 mg: 36 months
Broxil 125 mg/5 ml: 36 months

The prepared Broxil 125 mg/5 ml oral suspension should be refrigerated (2-8 ˚C) and can be kept for 14 days. Store the bottle with the prepared oral suspension in the outer packaging. Do not freeze.

6.4 Special precautions for storage

Store Broxil in a refrigerator in the outer packaging.

For storage conditions for the prepared Broxil oral suspension, see section 6.3.

6.5. Nature and contents of container

Broxil 250 mg and Broxil 500 mg
Container with 20 (2x10) capsules in PVC/PCTFE/alu blister

Broxil 125 mg/5 ml
Brown glass bottle with 30 grams of powder for oral suspension
The enclosed measuring cup is for measuring amounts from 5 ml up to 15 ml, respectively.
A syringe should be included for lower doses.

6.6 Special precautions for disposal

Reconstitution of Broxil suspension:

Tap to loosen the powder and then add 80 ml water. Shake well to create 100 ml suspension. Always shake the prepared oral suspension well before use.

7. MARKETING AUTHORISATION HOLDER

ACE Pharmaceuticals BV
Schepenveld 41
3891 ZK Zeewolde
The Netherlands
+31 (0)36-5474091 (medical information) ace@ace-pharm.nl

8. MARKETING AUTHORISATION NUMBER(S)

Broxil 250 mg:	RVG 04959
Broxil 500 mg:	RVG 09101
Broxil 125 mg/5 ml:	RVG 02672

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation/of latest renewal:

Broxil 250 mg:	30 June 1965/30 June 2015
Broxil 500 mg:	03 June 1982/03 June 2017
Broxil 125 mg/5 ml:	24 April 1968/24 April 2013

10. DATE OF REVISION OF THE TEXT

Latest partial change concerns section 2, December 2018