PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Ampiclox Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ampiclox Injection.
250 mg ampicillin as Ampicillin Sodium PhEur with 250 mg cloxacillin as Cloxacillin Sodium PhEur.

3. PHARMACEUTICAL FORM

Ampiclox Injection
Vials containing a sterile powder which on reconstitution is in a suitable form for parenteral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ampiclox is indicated for the treatment of infections in which susceptible organisms have been detected or are suspected (see Section 5.1):

- Surgery: post-operative wound infections, post-operative pulmonary infections
- Respiratory infections: bronchopneumonia, acute exacerbations of chronic bronchitis
- Obstetrics: puerperal fever
- Bacteraemia when associated with, or suspected to be associated with, any of the infections listed in 4.1.

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

4.2 Posology and method of administration

Intramuscular/ Intravenous
Adult dosage (including Elderly):
One to two vials every four to six hours.

Children’s dosage:
*Up to two years:*
Quarter adult dose

*Two to Ten years:*
Half adult dose.
Dosage may be further increased where necessary.

**ADMINISTRATION**

*500 mg vials*

**Intramuscular**
Dissolve vial contents in 1.5 ml Water for Injections BP.

**Intravenous**
Dissolve vial contents in 10 ml Water for Injections BP and administer slowly (three to four minutes). Ampiclox may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.

**Renal Impairment:**
In cases of renal failure, the dosage should be adapted in accordance with the following:

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dosing recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 mL/min</td>
<td>Normal dosing according to indication</td>
</tr>
</tbody>
</table>
| 50 to 10 mL/min      | Dosage (oral or parenteral administration) initial dose:
                          normal dose according to indication
                          Dosage (oral or parenteral administration) maintenance dose:
                          the normal unit dose (ampicillin-cloxacillin 500 mg orally up to 1 g IM or IV) three times daily |
| <10 mL/min           | Dosage (oral or parenteral administration) initial dose:
                          normal dose according to indication
                          Dosage (oral or parenteral administration) maintenance dose:
                          the normal unit dose twice or once daily |
| Haemodialysis        | In case of dialysis, an additional                                                   |
normal unit dose (ampicillin - cloxacillin 500 mg orally, up to 1 g IM. or IV) is to be administered after the procedure

Hepatic impairment
Reduce frequency of administration depending on the severity of the condition.

4.3. Contra-Indications

Penicillin hypersensitivity; ocular administration. Attention should be paid to possible cross-sensitivity with other beta-lactam antibiotics, e.g. cephalosporins, penicillins.

4.4 Special warnings and precautions for use

Before initiating therapy with ampiclox, careful enquiry should be made concerning previous hypersensitivity reactions to beta-lactams.

Caution should be observed when administering Ampiclox Injection to babies whose mothers are hypersensitive to penicillin.

Ampiclox should be avoided if infectious mononucleosis is suspected.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Dosage should be adjusted in patients with renal impairment (see section 4.2).

Sodium Content
One gram of this medicinal product contains 60 mg of sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other Medicinal Products and other Forms of Interaction

Concomitant use of allopurinol during treatment with ampicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of Ampiclox and allopurinol.
In common with other antibiotics, Ampiclox may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Therefore, alternative non-hormonal methods of contraception are recommended.

Concurrent use with probenecid may result in increased and prolonged blood levels of Ampiclox.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

4.6. Pregnancy and Lactation

Animal studies have shown no teratogenic effects. The product has been in clinical use since 1968 and the limited number of reported cases of use in human pregnancy has shown no evidence of untoward effect. The use of Ampiclox in pregnancy should be reserved for cases considered essential by the clinician. During lactation, trace quantities of penicillins can be detected in breast milk.

4.7. Effects on Ability to Drive and Use Machines

None known.

4.8 Undesirable effects

The following statements reflect the information available on the adverse reaction profile of the individual constituents (ampicillin and cloxacillin) and/or the combination in AMPICLOX. The majority of the adverse reactions listed below are not unique to AMPICLOX and may occur when using other penicillins.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000), including isolated reports.

Common and uncommon adverse reactions were generally determined from pooled safety data from a clinical population of 1210 treated patients. Rare and very rare adverse reactions were generally determined from more than 32 years of post-marketing experience data and refer to reporting rate rather than true frequency.

Blood and lymphatic system disorders
Very rare: Haemolytic anaemia, leucopenia, thrombocytopenia and agranulocytosis.

**Immune system disorders**  
Very rare: Anaphylaxis (see item 4.4 Warnings) and other hypersensitive reactions.

Skin disorders and interstitial nephritis have been reported as hypersensitivity reactions. (See also Skin and subcutaneous tissue disorders and Renal and urinary disorders).  
If any hypersensitivity reaction occurs, the treatment should be discontinued.

**Nervous system disorders**  
Very rare: Myoclonus and convulsions.

**Gastrointestinal disorders**  
Common: Diarrhoea and nausea.  
Uncommon: Vomiting.  
Very rare: Pseudomembranous colitis (see Warnings and Precautions) and haemorrhagic colitis.

**Hepato-biliary disorders**  
Very rare: Hepatitis and cholestatic jaundice. A moderate and transient increase in transminases.

**Skin and subcutaneous tissue disorders**  
Common: Skin rash, urticaria and pruritus.  

The incidence of skin rash, pruritus and urticaria is higher in patients suffering from infectious mononucleosis and acute or chronic leukaemia of lymphoid origin.

Very rare: Bullous reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), exfoliative dermatitis and purpura.

Skin disorders have also been reported as hypersensitivity reactions (see Immune system disorders)

**Renal and urinary disorders**  
Very rare: Interstitial nephritis.

Interstitial nephritis has also been reported as a hypersensitivity reaction. (See also Immune system disorders)

**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 reaction via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Overdosage with oral ampicillin - cloxacillin is unlikely to cause serious reactions if renal function is normal. Very high dosage of i.v. administered ampicillin and/or high dosage of cloxacillin in renal failure may provoke neurotoxic reactions similar to those seen with benzylpenicillin in excess. Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident.

Gastrointestinal effects should be treated symptomatically. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Penicillins with extended spectrum

ATC code: J01CA51

Ampiclox is a combination of ampicillin, a broad spectrum antibiotic and cloxacillin, a semi-synthetic beta-lactamase resistant penicillin with activity against gram-negative and gram-positive bacteria including beta-lactamase producing staphylococci.

Both ampicillin and cloxacillin are bactericidal antibiotics and act by interfering with the formation of new bacterial cell wall by dividing organisms.

Mechanism of resistance
The main mechanism of resistance to ampicillin/cloxacillin is alteration of penicillin-binding proteins (PBPs), which reduce the affinity of the antibacterial agent for the target.

Ampiclox breakpoints

<table>
<thead>
<tr>
<th>EUCAST Interpretive Criteria</th>
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<tbody>
<tr>
<td><strong>Ampicillin MIC breakpoint (mg/L)</strong></td>
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</tbody>
</table>
### Pharmacodynamic Effects

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

The cloxacillin component of ampiclox covers exclusively the suspected or demonstrated presence of *Staphylococcus aureus*. Methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin susceptible coagulase-negative staphylococci (MSCoNS) are commonly susceptible to cloxacillin. MRSA and MRCoNS are resistant to cloxacillin. For all other indicated bacterial species, the susceptibility of ampicillin/cloxacillin is similar to ampicillin including limited activity against Gram-negative organisms.

### In vitro susceptibility of micro-organisms to Ampicillin

<table>
<thead>
<tr>
<th>Commonly Susceptible Species</th>
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</thead>
<tbody>
<tr>
<td>Gram-positive aerobes:</td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
</tr>
<tr>
<td>Beta-hemolytic streptococci</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td>Gram-negative aerobes:</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
</tr>
</tbody>
</table>

**Species for which acquired resistance may be a problem**

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
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<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td></td>
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<tr>
<td><em>Haemophilus influenzae</em></td>
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<tr>
<td><em>Salmonella</em> spp.</td>
<td></td>
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<tr>
<td><em>Shigella</em> spp.</td>
<td></td>
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<tr>
<td><em>Neisseria gonorrhoeae</em></td>
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<tr>
<td><em>Pasteurella</em> spp.</td>
<td></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
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<tr>
<td><em>Vibrio cholerae</em></td>
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</table>

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
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</thead>
<tbody>
<tr>
<td><em>Corynebacterium</em> spp.</td>
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</tr>
<tr>
<td><em>Staphylococcus</em> spp. including <em>Staphylococcus aureus</em></td>
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<tr>
<td><em>Streptococcus pneumoniae</em></td>
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<tr>
<td>Viridans group streptococcus</td>
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</table>

<table>
<thead>
<tr>
<th>Gram-positive anaerobes:</th>
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<tbody>
<tr>
<td><em>Clostridium</em> spp.</td>
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</table>

<table>
<thead>
<tr>
<th>Gram-negative anaerobes:</th>
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</thead>
<tbody>
<tr>
<td><em>Prevotella</em> spp.</td>
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</table>

**Inherently resistant organisms**

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
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<tbody>
<tr>
<td><em>Acinetobacter baumanii</em></td>
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<tr>
<td><em>Burkholderia cepacia</em></td>
<td></td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
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<tr>
<td><em>Citrobacter koseri</em></td>
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<tr>
<td><em>Enterobacter aerogenes</em></td>
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<tr>
<td><em>Enterobacter cloacae</em></td>
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<tr>
<td><em>Escherichia hermanii</em></td>
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<tr>
<td><em>Hafnia alvei</em></td>
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<tr>
<td><em>Klebsiella pneumoniae</em></td>
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<tr>
<td>Morganella morganii</td>
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<td>-------------------------------------</td>
<td></td>
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<tr>
<td>Proteus penneri</td>
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<tr>
<td>Proteus vulgaris</td>
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<tr>
<td>Providencia rettgeri</td>
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<tr>
<td>Providencia stuartii</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>Serratia marcescens</td>
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<tr>
<td>Stenotrophomonas maltophilia</td>
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<tr>
<td>Yersinia enterocolitica</td>
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</tbody>
</table>

5.2. **Pharmacokinetic Properties**

Ampicillin has a plasma half-life of approximately 1-2 hours and is excreted mainly in the bile and urine.

Cloxacillin is excreted in the urine and bile with a serum half-life of approximately 30 minutes.

5.3. **Pre-clinical Safety Data**

Not applicable.

6. **Pharmaceutical Particulars**

6.1. **List of Excipients**

None.

6.2. **Incompatibilities**

Ampiclox Injection should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates) or with intravenous lipid emulsions.

If Ampiclox is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside and possibly precipitation can occur under these conditions.
6.3. Shelf-Life

36 months.

6.4. Special Precautions for Storage

Ampiclox Injection should be stored in a cool dry place.

6.5. Nature and Content of Container

Clear glass vials supplied in boxes of 10 vials with instructions for use.

6.6. Instructions for Use, Handling and Disposal

Ampiclox 500 mg Injection may be added to most intravenous fluids (e.g. Water for Injections, sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%). In intravenous solutions containing glucose or other carbohydrates, Ampiclox should be infused within one hour of preparation. Intravenous solutions of Ampiclox in Water for Injections or sodium chloride 0.9% should be infused within 24 hours of preparation. Full particulars are given in the Package Enclosure Leaflet. Preparation of Ampiclox infusion solutions must be carried out under appropriate aseptic conditions if these extended storage periods are required.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Beecham Group plc
980 Great West Road
Brentford
Middlesex
TW8 9GS

Trading as:

Beecham Research or SmithKline Beecham Pharmaceuticals at:
8. MARKETING AUTHORISATION NUMBER

PL 00038/5003R

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

3 June 1987 / 24 July 1997

10 DATE OF REVISION OF THE TEXT

11/11/2014