**AUSTRALIAN PRODUCT INFORMATION**

# CILAMOX

*amoxicillin trihydrate capsule & powder for oral liquid*

## 1 NAME OF THE MEDICINE

Amoxicillin trihydrate

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CILAMOX capsule contains 250 mg or 500 mg of amoxicillin (as trihydrate) as the active ingredient.

CILAMOX SUGAR FREE SYRUP powder for oral liquid contains 125 mg/5 mL or 250 mg/5 mL of amoxicillin (as trihydrate) as the active ingredient.

Excipients of known effect (powder for oral liquid only): saccharin, benzoates and sorbitol.

For the full list of excipients, see section 6.1 List of Excipients.

## 3 PHARMACEUTICAL FORM

CILAMOX 250 mg capsules are size 1 hard gelatin capsules that are opaque white in colour.

CILAMOX 500 mg capsules are size 0 hard gelatin capsules that are opaque white in colour.

CILAMOX SUGAR FREE SYRUP 125 mg/5 mL and 250 mg/5 mL powder for oral liquid is a white to off-white free flowing powder with characteristic fruity odours.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

CILAMOX is indicated for the treatment of infections due to susceptible strains of the sensitive organisms:

**Gram-negative**

*H. influenzae*, *E. coli*, *Pr. mirabilis*, and *N. gonorrhoeae*.

**Gram-positive**

Streptococcus species, *S. pneumoniae*, non-penicillinase producing Staphylococci and *Bacillus anthracis*.

Note 1: CILAMOX may be useful in instituting therapy prior to bacteriology; however, bacteriological studies to determine the causative organisms and their sensitivity to CILAMOX should be performed.

Note 2: Penicillins are now generally regarded only as adjunctive to some other established first-line antibiotic therapy in the treatment and post-exposure prophylaxis of anthrax, because of concerns of constitutive and inducible beta-lactamase in *Bacillus anthracis*. If use of amoxicillin is contemplated, appropriate bacteriological studies must be performed by a reliable and established test method. Amoxicillin may then be suitable if the specific *B. anthracis* strain has been shown definitively to be sensitive to penicillin/amoxicillin.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

The following recommended doses are for patients with normal renal function. The dosage in patients with renal impairment may need to be adjusted (see section 4.4 Special Warnings and Precautions for Use – Use in Renal Impairment).

**Upper respiratory tract infections** (due to *Streptococci*, *pneumococci*, non-penicillinase producing *Staphylococci* and *H. influenzae*)

**Genito-urinary tract infections** (due to E. coli, Proteus mirabilis and Strep. faecalis)

**Skin and skin structure infections** (due to *Streptococci*, sensitive *Staphylococci* and *E. coli*):

- *Adults*: 250 mg every eight hours
- *Children*: (under 20 kg): 25 mg/kg/day in equally divided doses every eight hours

In severe infections or those caused by less susceptible organisms, 500 mg every eight hours for adults and 50 mg/kg/day in equally divided doses every 8 hours for children may be needed.

**Lower respiratory tract infections** (due to *Streptococci*, *pneumococci*, non-penicillinase producing *Staphylococci* and *H. influenzae*):

- *Adults*: 500 mg every eight hours
- *Children*: (under 20 kg): 50 mg/kg/day in equally divided doses every eight hours

**Urethritis** (due to *N. gonorrhoeae*):

- *Adults*: 3 grams as a single dose. Cases of gonorrhoea with a suspected lesion of syphilis should have dark field examinations before receiving CILAMOX and monthly serological tests for a minimum of four months

**Acute, uncomplicated lower urinary tract infections** (due to *E. coli*, *Proteus mirabilis*, *Strep. faecalis* and non-penicillinase producing *Staphylococci*):

- *Adults*: 3 grams as a single dose

It should be recognised that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days treatment for any infection caused by haemolytic Streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**Cutaneous anthrax** (due to non-penicillinase producing *B. anthracis*) proven to be susceptible to amoxicillin and without systemic symptoms and not located on the head or neck and not associated with extensive oedema. For more complicated cases, the advice of an infectious disease specialist should be sought.

- *Adults:* 500 mg every eight hours
- *Children*: (under 20 kg): 80 mg/kg/day in equally divided doses every eight hours

**Post-exposure anthrax prophylaxis** (due to non-penicillinase producing *B. anthracis*) proven to be susceptible to amoxicillin:

- *Adults*: 500 mg every eight hours
- *Children*: (under 20 kg): 80 mg/kg/day in equally divided doses every eight hours

The recommended treatment period for cutaneous anthrax and post-exposure anthrax prophylaxis should be 60 days. Periodic assessment of organ system functions is advisable (see section 4.4 Special Warnings and Precautions for Use). In the case of cutaneous anthrax which is clearly and unequivocally the result of a

zoonotic mode of transmission and in which there are no systemic symptoms, treatment for shorter periods of time may still be an option.

Note: The children's dosage is intended for individuals whose weight will not cause the dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

## 4.3 CONTRAINDICATIONS

Individuals with a history of an allergic reaction to the penicillins. It is also contraindicated in patients with a history of amoxicillin associated hepatic dysfunction or jaundice.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including CILAMOX. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. *Clostridium difficile* associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents and may range in severity from mild diarrhoea to fatal colitis. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered.

Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

### Prolonged Therapy

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable.

### Superinfections

Superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Aerobacter, Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

### Infectious Mononucleosis

CILAMOX, an aminopenicillin, is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis in the presence of which there is a high incidence of rash if amoxicillin is used.

### Lymphatic Leukaemia

CILAMOX should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to ampicillin-induced skin rashes.

### Use in Hepatic Impairment

Cholestatic hepatitis, which may be severe but is usually reversible, has been reported. Signs and symptoms may not become apparent until several weeks after treatment has ceased. In most cases resolution has occurred with time. However, in extremely rare circumstances, deaths have been reported. These have almost always been cases associated with serious underlying disease or concomitant medications. Hepatic events subsequent to CILAMOX have occurred predominantly in adults and elderly patients.

CILAMOX should be used with care in patients with evidence of hepatic dysfunction.

### Use in Renal Impairment

The dosage should be adjusted in patients with moderate or severe renal impairment. In renal impairment the excretion of the antibiotic will be delayed, and depending on the degree of impairment, it may be necessary to reduce the total daily dosage.

### Use in the Elderly

No data available.

### Paediatric Use

No data available.

### Effects on Laboratory Tests

Oral administration of CILAMOX results in high concentrations of amoxicillin in the urine. Since high urine concentrations of ampicillin may yield false reactions when testing for the presence of glucose in urine using *Clinitest*, Benedict's solution or Fehling's solutions it is therefore recommended that tests based on enzymatic glucose oxidase reactions such as *Clinistix* or *Tes-Tape* should be used.

A transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol was observed following administration of ampicillin to pregnant women. This effect may also occur with amoxicillin.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

### Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with CILAMOX may result in increased and prolonged blood levels of amoxicillin.

### Allopurinol

The concurrent administration of allopurinol and ampicillin causes substantial increases in the incidence of rashes compared to administration of ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

Similar reactions can be expected with amoxicillin.

### Oral Contraceptives

In common with other broad-spectrum antibiotics, patients should be warned that CILAMOX may reduce the effectiveness of oral contraceptives.

### Warfarin

In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ration should be carefully monitored with the addition or withdrawal of amoxicillin.

### Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on Fertility

No data available.

### Use in Pregnancy

Pregnancy category: A

No teratogenic effects were observed in animal studies using oral or parenteral preparations of amoxicillin. Extensive clinical use since 1972 and suitability in human pregnancy has been well documented in clinical/ studies.

#### Use in Labour and Delivery/

Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased uterine tone, frequency, height, and duration of contractions. However, it is not known whether the use of CILAMOX in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetric intervention or resuscitation of the newborn will be necessary.

### Use in Lactation

Amoxicillin is excreted in breast milk; therefore, caution should be exercised if CILAMOX is administered to a breast-feeding mother.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins.

The following reactions have been reported as associated with the use of CILAMOX:

*Infections and infestations:* mucocutaneous candidiasis have been reported very rarely.

*Gastrointestinal Effects*: diarrhoea, nausea, vomiting. Intestinal candidiasis and antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis) have been reported rarely. Black hairy tongue has been reported very rarely (see section 4.4 Special Warnings and Precautions for Use).

*Hypersensitivity Reactions:* erythrematous maculopapular rashes, pruritus and urticaria have been reported occasionally. Rarely, skin reactions such as erythema multiforme and Steven-Johnsons syndrome, toxic epidermal necrolysis, and bullous, exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. As with other antibiotics, severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness, hypersensitivity vasculitis and interstitial nephritis have been reported rarely. Whenever such reactions occur, CILAMOX should be discontinued. (Note: Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids).

*Hepatic Effects:* a moderate rise in AST has been noted, but the significance of this finding is unknown. As with other beta-lactam antibiotics, hepatitis and cholestatic jaundice have been reported rarely.

*Haematological Effects:* reactions such as anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia (including severe neutropenia or agranulocytosis) have been reported during therapy with other penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Prolongation of bleeding time and prothrombin time have also been reported rarely.

*Renal and urinary tract disorders*: interstitial nephritis, crystalluria (see Section 4.9 Overdose).

*CNS effects*: CNS effects have been seen rarely. They include aseptic meningitis, hyperkinesia, dizziness, and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

*Miscellaneous*: Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

### Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water/electrolyte imbalance should be treated symptomatically. During the administration of high doses of amoxicillin, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria. Amoxycillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special Warnings and Precautions for Use).

If a large overdose is ingested, the patient should be kept under observation and appropriate treatment should be given as considered necessary.

Amoxicillin may be removed from the circulation by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of Action

CILAMOX differs *in-vitro* from benzylpenicillin in the Gram-negative spectrum and has the same Gram-positive and Gram-negative spectrum as ampicillin.

*In-vitro*, most strains of *Haemophilus influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis* and Salmonellae are sensitive to CILAMOX at serum concentrations which may be expected following the recommended doses.

*Esherichia coli* isolate are becoming increasingly resistant to amoxicillin *in-vitro* due to the presence of penicillinase-producing strains.

Strains of gonococci which are relatively resistant to benzylpenicillin may be sensitive to CILAMOX.

*In-vitro* studies have demonstrated the sensitivity of most strains of the following Gram-positive bacteria; alpha- and beta-haemolytic Streptococci, *Streptococcus pneumoniae*, non-penicillinase producing Staphylococci, *Streptococcus faecalis* and *Bacillus anthracis*. However, some of the organisms were sensitive to CILAMOX only at concentrations achieved in the urine.

CILAMOX is not effective against penicillinase producing bacteria, particularly resistant Staphylococci, which now have high prevalence. All strains of Pseudomonas and most strains of Klebsiella and Aerobacter are resistant.

Like benzylpenicillin, CILAMOX is bactericidal against sensitive organisms during the stage of active multiplication. It is believed to act through the inhibition of biosynthesis of cell wall mucopeptide.

A commonly used method involving flooding culture plates with a large inoculum of organisms, has demonstrated that a 15 mm or greater inhibition zone represents sensitivity using a 25 microgram disc of amoxicillin.

### Clinical Trials

No data available.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

CILAMOX is stable in the presence of gastric acid and is rapidly and well absorbed after oral administration, even in the presence of food. It diffuses rapidly into most body tissues and fluids, with the exception of brain and spinal fluid except when the meninges are inflamed.

### Distribution

CILAMOX is not highly protein-bound, being only 17% protein-bound in serum as compared to 59% for benzylpenicillin. The average peak serum levels resulting from the oral administration of CILAMOX are approximately double those compared to the same dose of ampicillin. Peak serum levels of amoxicillin are approximate following intramuscular administration of the same dose of ampicillin. Oral peak serum levels are reached after 1 to 2 hours. Measurable serum levels of CILAMOX are present even at 8 hours after administration. The area under the curve (AUC) for CILAMOX is twice that of ampicillin given in the same dose and by the oral route. About 60 to 70% of an oral dose of CILAMOX is excreted in the urine as compared to 30 to 40% with ampicillin given by the same route and in the same dose.

### Excretion

CILAMOX has been shown to diffuse into sputum and saliva and is excreted mainly via the urine where it exists in high concentration. The amount to be found in the bile is variable depending on normal biliary secretory function.

The half-life of CILAMOX is approximately one hour (61.3 minutes) with normal renal function and in the absence of renal function 16 to 20 hours.

CILAMOX is excreted in the urine both unchanged and as penicilloic acid. With normal renal function, about 75% of a 1 gram dose is excreted in the urine in 6 hours (60% is biologically active and 15% is penicilloic acid). However, about 32% of a 3 gram dose is excreted via the urine as the biologically active component in 8 hours (by which time most of the urinary excretion is complete). This proportional difference in the amount excreted from the different doses reflects a lack of linearity between doses and the extent of absorption with a levelling off at higher doses of oral amoxicillin.

Excretion of amoxicillin can be delayed by concurrent administration of probenecid, thus prolonging its therapeutic effect.

Following oral administration, the finding of higher peak serum concentrations, larger AUC, and greater urinary excretion of CILAMOX, with identical half-lives for the two antibiotics, all reflect much better absorption of CILAMOX.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

No data available.

### Carcinogenicity & Mutagenicity

Long-term carcinogenicity or mutagenicity studies have not been carried out in animals to determine carcinogenic or mutagenic potential of CILAMOX.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

CILAMOX 250 mg and 500 mg capsules contain the following inactive ingredients: gelatin, titanium dioxide, magnesium stearate and purified talc.

CILAMOX SUGAR FREE SYRUP powder for oral liquid contain the following inactive ingredients: colloidal anhydrous silica, disodium edetate, saccharin sodium, silicon dioxide, sodium benzoate, sorbitol, xanthan gum and the following flavours – Banana 51464 AP0572 (ARTG PI No:: 2737) and Forest Berry 502874 AP0572 (ARTG PI No: 2738) [125 mg/5 mL] and Sonaflo Passion Fruit 171011 (ARTG PI No: 108517) and Sonaflo Vanilla 080911 (ARTG PI No: 108516) [250 mg/5 mL].

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Capsules: Store below $25^0$C.

Powder for oral liquid: Store below $25^0$C. Protect from light, heat and moisture.

## 6.5 NATURE AND CONTENTS OF CONTAINER

Container type:

- *Capsules:* blister pack (PVC/PVDC/Al)
- *Powder for oral liquid:* HDPE bottle with polypropylene child resistant cap

Pack sizes:

- *Capsules:* 3, 20
- *Powder for oral liquid:* 100 mL

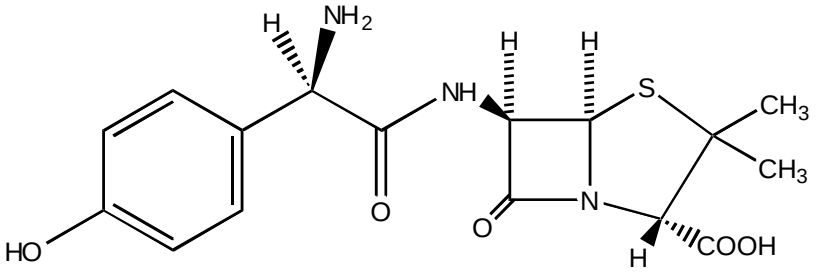
Some strengths, pack sizes and/or pack types may not be marketed.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical Structure**




,$3H_2O$

Chemically amoxicillin trihydrate is D-(-)-α-amino-ρ-hydroxybenzylpenicillin trihydrate which is susceptible to hydrolysis by β-lactamases.

Molecular formula: $C_{16}H_{19}N_3O_5S.3H_2O$

Molecular weight: 419.5

Solubility: slightly soluble in water and ethanol (96%); practically insoluble in chloroform, ether and fixed oils. It dissolves in dilute solutions of acids and of alkali hydroxides.

**CAS Number**

61336-70-7

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

# 8 SPONSOR

**Viatris Pty Ltd**

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 314 527

# 9 DATE OF FIRST APPROVAL

Capsules: 15/05/2017

Powder for oral liquid: 11/02/1997

# 10 DATE OF REVISION

25/01/2022

### Summary Table of Changes

| Section Changed | Summary of New Information |
|---|---|
| **4.4** | Addition of *Clostridium difficile* associated diarrhoea (CDAD) warning<br>Addition of abnormal prolongation of prothrombin time warning |
| **4.5** | Addition of warfarin interaction<br>Addition of tetracycline interaction |
| **4.8** | Addition of infections and infestations, renal and urinary tract disorders, CNS effects and miscellaneous adverse effects<br>Update to gastrointestinal effects, hypersensitivity reactions, hepatic effects, and haematological effects |
| **4.9** | Addition of overdose gastrointestinal effects |
| **2, 4.8, 6.1, 6.4, 6.5** | Editorial Change |
| **8** | Update to Sponsor details |

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