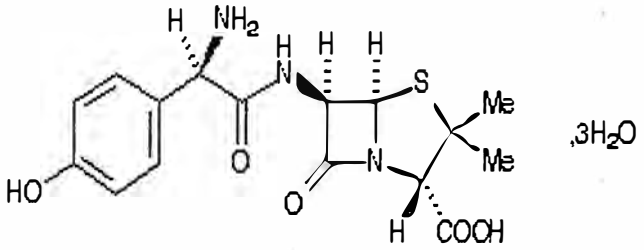
AUGMENTIN® XR 1000/62.5 TABLETS

PRODUCT INFORMATION

(Amoxycillin Trihydrate, Amoxycillin Sodium and Potassium Clavulanate)

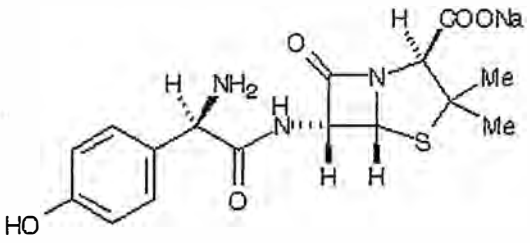
DESCRIPTION

AUGMENTIN XR 1000/62.5 tablets is a combination product containing the semisynthetic antibiotic, amoxycillin (as the trihydrate and as the sodium salt) and the β-lactamase inhibitor, potassium clavulanate. Chemically, amoxycillin is D-(-)-α-amino-p-hydroxybenzylpenicillin. It is susceptible to hydrolysis by β-lactamases. Amoxycillin trihydrate may be represented structurally as:



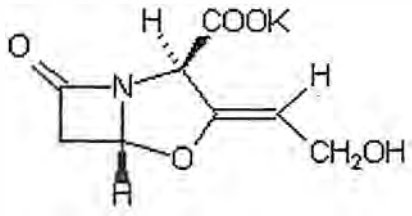
CAS – 61336-70-7.

Amoxycillin sodium may be represented structurally as:



CAS – 34642-77-8

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is an irreversible inhibitor of many β-lactamase enzymes except type 1 (Richmond). It is a β-lactam compound with only weak antibacterial activity. Chemically potassium clavulanate is potassium *Z*-(2*R*,5*R*)-3-(ß-hydroxyethylidene) clavam-2-carboxylate, and may be represented structurally as:



CAS – 61177-45-5.

AUGMENTIN XR 1000/62.5 is a sustained release tablet that provides an extended amoxycillin pharmacokinetic profile. The AUGMENTIN XR 1000/62.5 formulation extends the spectrum of

AUGMENTIN to include the majority of *S. pneumoniae* where resistance is mediated by penicillin-bin ıg proteins (penicillin-resistant *S. pneumoniae* (PRSP) and macrolide-resistant *S. pneumoniae* (MRSP)).

AUGMENTIN XR 1000/62.5 tablets also contain the inactive ingredients: anhydrous citric acid, colloidal anhydrous silica, hypromellose, magnesium stearate, microcrystalline cellulose, macrogol, sodium starch glycollate, titanium dioxide and xanthan gum.

PHARMACOLOGY

Pharmacokinetics

Absorption

Amoxycillin is stable in the presence of gastric acid. Their two components are rapidly absorbed if administered immediately before or with a meal, but if given after meals, the serum levels of clavulanic acid are significantly reduced. To optimise absorption of clavulanic acid AUGMENTIN XR 1000/62.5 tablets should be administered at the start of a meal. The pharmacokinetics of amoxycillin are not affected by food.

The pharmacokinetics of the components of AUGMENTIN XR 1000/62.5 tablets following oral administration of two AUGMENTIN XR 1000/62.5 (total dose of 2g/125mg) tablets at the start of a standardised meal are presented in the table below.

Table 1: Mean (SD) Pharmacokinetic Parameters for Amoxycillin and Clavulanate Following Oral Administration of Two AUGMENTIN XR 1000/62.5 Tablets (2000/125mg) to Healthy Adult Volunteers [n = 55] Fed a Standardised Meal

Parameter (units)	Amoxycillin	Clavulanate
Dose (mg)	2000	125
T>MIC 4μg/mL (hours) [%]	5.9 [49.4]	N/A
AUC(0-inf) (μg.h/mL)	71.6 (16.5)	5.29 (1.55)
C_{max} (μg/mL)	17.0 (4.0)	2.05 (0.80)
T_{max} (hours)†	1.50 (1.00-6.00)	1.03 (0.75-3.00)
$T_{1/2}$ (hours)	1.27 (0.20)	1.03 (0.17)

†median (range).

Distribution

Following oral administration, both amoxycillin and clavulanic acid have been shown to diffuse in significant concentrations into pus, bile, and pleural, synovial and peritoneal fluids. Both penetrate poorly into the cerebrospinal fluid (CSF) when the meninges are normal. Amoxycillin penetrates into the CSF better through inflamed meninges, but the maximum concentrations are still much lower than the peak serum levels. There are no data at present on the CSF penetration of clavulanic acid in patients with meningeal inflammation.

Neither amoxycillin nor clavulanic acid is highly protein bound. Studies show that about 25% for clavulanate and 18% for amoxycillin of total plasma drug content is bound to protein. From animal studies, there is no evidence to suggest either component accumulates in any organ.

Elimination

As with other penicillins, renal excretion is the major route of amoxycillin clearance, while clavulanate elimination is via both renal and non-renal mechanisms. Approximately 70% of the dose of amoxycillin is excreted in urine as amoxycillin. For clavulanic acid, following the administration of 125mg of radio-labelled potassium clavulanate orally to normal volunteers 68% of the administered radioactivity was recovered in the urine in 24 hours. Of this 34% (ie. 23% of the administered dose) represented unchanged clavulanic acid.

2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid (the major metabolite) and 1-amino-4-hydroxy-butan-2-one accounted for a further 23% and 12% (ie. 16% and 8% respectively of the administered dose). Small amounts of other yet unidentified metabolites were also present. These metabolites were also present in the urine of rat and dog. The extent of urinary excretion of clavulanic acid and its metabolites is lower in rat urine than in dog and human urine.

Concurrent administration of probenecid delays amoxycillin excretion but does not delay renal excretion of clavulanic acid.

CLINICAL TRIALS

An extensive worldwide Phase III clinical program, comprising five pivotal controlled studies and three supporting uncontrolled studies, was conducted to evaluate the efficacy and safety of AUGMENTIN XR 1000/62.5 tablets for the treatment of community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) in adults.

The dose of AUGMENTIN XR 1000/62.5 tablets used in all trials was 2000/125mg bd. This was determined by a combination of known PK/PD targets and the Phase I pharmacokinetic studies.

Community –Acquired Pneumonia (CAP)

The four pivotal studies (546, 556, 557 and 600) were all randomised, double-blind, double-dummy, parallel group studies designed to assess the clinical and bacteriological efficacy and safety of oral AUGMENTIN XR 2000/125mg bd in the treatment of patients with CAP, in comparison with the currently approved formulations of AUGMENTIN. Study 557, (AUGMENTIN 875/125mg tds for 7 or 10 days); Study 556, (AUGMENTIN 1000/125mg tds for 10 days) and Studies 546 and 600, (AUGMENTIN 875/125mg bd for 7 days).

In studies 557 and 556 the sample size was calculated assuming an underlying equivalent clinical response rate of 85% at test of cure (TOC), and the non-inferiority limit was set at -15%. In 546, the sample size was calculated assuming an underlying equivalent clinical response rate of 90% at TOC, and the non-inferiority limit was set at -10%. In study 600, the sample size was calculated assuming an underlying equivalent clinical response rate of 88% at TOC, and the non-inferiority limit was set at -10%.

Three of the pivotal studies (557, 556 and 600) demonstrated non-inferiority of AUGMENTIN 2000/125 bd in comparison with current formulations and regimens of AUGMENTIN Duo Forte 875/125 bd or tds and AUGMENTIN 1000/125 tds. In the 4th study (546) non-inferiority at a limit of –10% was not demonstrated for AUGMENTIN 2000/125 bd in comparison with AUGMENTIN 875/125 bd.. Clinical and bacteriological success rates at test of cure for the PP and ITT populations in the principal studies 557, 556, 546 and 600 are presented in the table below, together with treatment differences and corresponding 95% CIs.

Table 2: Summary of Clinical and Per Patient Bacteriological Responses at Test of Cure: Principal CAP Studies

	Success Rate		
	Augmentin XR* % (n/N)	Augmentin** % (n/N)	Treatment Difference % (95% CI)†
CLINICAL RESPONSE (PRIMARY VARIABLE)			
Clinical PP Population			
557	94.7 (108/114)	88.8 (103/116)	5.9 (-1.1, 13.0)
556	91.5 (108/118)	93.0 (106/114)	-1.5 (-8.3, 5.4)
546	86.3 (176/204)	91.2 (186/204)	-4.9 (-11.0, 1.2)
600	90.3 (223/247)	87.6 (198/226)	2.7 (-3.0, 8.3)
547	85.5 (712/833)	-	- (82.9, 87.8)
ITT Population			
557	84.8 (134/158)	77.0 (124/161)	7.8 (-0.8, 16.4)
556	81.1 (137/169)	85.7 (150/175)	-4.6 (-12.5, 3.2)
546	78.0 (199/255)	82.6 (214/259)	-4.6 (-11.4, 2.3)
600	85.1 (274/322)	78.1 (243/311)	7.0 (0.9, 13.0)
547††	76.4 (848/1110)	-	- (73.8, 78.8)
PER PATIENT BACTERIOLOGICAL RESPONSE			
Bacteriology PP Population			
557	85.0 (17/20)	77.3 (17/22)	7.7 (-15.8, 31.2)
556	90.6 (29/32)	84.4 (27/32)	6.3 (-9.9, 22.4)
546	78.1 (25/32)	84.6 (22/26)	-6.5 (-26.4, 13.4)
600	86.6 (58/67)	78.4 (40/51)	8.1 (-5.8, 22.1)
547††	83.0 (225/271)	-	(77.9, 87.2)
Bacteriology ITT Population			
557	70.0 (21/30)	66.7 (20/30)	3.3 (-20.2, 26.9)
556	84.1 (37/44)	76.6 (36/47)	7.5 (-8.7, 23.7)
546	69.2 (27/39)	83.3 (25/30)	-14.1 (-33.8, 5.6)
600	83.9 (73/87)	67.1 (49/73)	16.8 (3.5, 30.0)
547	78.1 (267/342)	-	(73.2, 82.3)

* Augmentin XR 2000/125mg bd; treatment duration was 7 days in study 546 and 600, 10 days in study 556, 7 or 10 days in study 557 and 7 days in studies 547.

** Augmentin comparators are Augmentin 875/125mg bd in studies 546 and 600, Augmentin 875/125mg tds in study 557 and Augmentin 1000/125mg tds in study 556.

† Limits of non-inferiority for the primary efficacy variable (clinical response at test of cure) were prospectively defined as≥-15% for studies 557 and 556 and ≥-10% for studies 546 and 600.

†† Study 547 – primary response is the per patient bacteriological efficacy and the clinical response is a secondary efficacy parameter

An analysis by country grouping, indicated that the overall result of study 546 was influenced by a small group of non-USA patients (84/204, 42.2%) who had an unusually high clinical response at TOC (96.6%) in the Augmentin 875/125mg bd group compared with the AUGMENTIN XR 1000/62.5 group (86.7%). However, in the larger USA patient group, the clinical response at TOC was similar in both treatment groups (AUGMENTIN XR 1000/62.5: 86.0%, Augmentin 875/125mg bd 87.2%) with the non-inferiority criterion of –10% achieved (95% CI: -9.9, 7.4).

Bacteriological efficacy of AUGMENTIN XR 1000/62.5 was demonstrated in the non-comparative study 547 with a high per patient bacteriological success rate for the bacteriology PP population success rate of 83.0% (n=271) (95% CI: 77.9, 87.2). AUGMENTIN XR 1000/62.5 was particularly effective in the subgroup of patients with infection due to *S. pneumoniae*, with a bacteriological response rate at TOC of 91.6% (95% CI: 85.1%, 95.5%) in the bacteriology PP population.

Acute Bacterial Sinusitis (ABS)

The pivotal study conducted in ABS (Study 550) was a randomised, double-blind, double-dummy, multicentre, parallel group study designed to assess the clinical and bacteriological efficacy and safety of oral AUGMENTIN XR 2000/125mg twice daily for 10 days versus oral levofloxacin 500mg once daily for 10 days in the treatment of patients with clinically and radiologically confirmed ABS. In addition, two supporting, non-comparative studies (551 and 592) were conducted to assess the bacteriological and clinical efficacy of AUGMENTIN XR 1000/62.5 for 10 days in the treatment of patients with ABS, particularly those with PRSP.

The primary efficacy variable (in study 550) was combined clinical and radiological response (success, failure or unable to determine) at TOC. The combined response was defined as success if the patient was a clinical success and there was an improvement or no change in the radiological signs of ABS. The lower limit of non-inferiority for the primary efficacy variable was prospectively defined as $\geq$ - 15%. The primary efficacy variable for the non-comparator studies (551 and 592) was bacteriological response at TOC.

Study 550 demonstrated non-inferiority for the primary efficacy variable of AUGMENTIN 2000/125 bd for 10 days in comparison with oral levofloxacin 500mg od for 10 days.

Combined clinical/radiological, clinical and bacteriological success rates at the test of cure visit for the PP and ITT populations in the principal study 550 are presented in the Table below, together with treatment differences and 95% CIs, where appropriate.

Table 3 Combined Clinical/Radiological, Clinical and Bacteriological Responses at the Test of Cure Visit: Principal ABS Study 550

	Success Rate		Treatment Difference
	Augmentin XR 2000/125mg bd (10 days)	Levofloxacin 500mg od (10 days)	
	% (n/N)	% (n/N)	% (95% CI)*
CLINICAL/RADIOLOGICAL RESPONSE (PRIMARY VARIABLE)			
Clinical PP Population	83.7 (103/123)	84.3 (118/140)	-0.5 (-9.4, 8.3)
ITT Population	76.4 (136/178)	83.0 (151/182)	-6.6 (-14.9, 1.7)
CLINICAL RESPONSE			
Clinical PP Population	87.0 (107/123)	88.6 (124/140)	-1.6 (-9.5, 6.4)
ITT Population	82.0 (146/178)	88.5 (161/182)	-6.4 (-13.7, 0.9)
BACTERIOLOGICAL RESPONSE			
Bacteriology PP Population	93.3 (14/15)	100.0 (10/10)	**
Bacteriology ITT Population	90.0 (18/20)	93.3 (14/15)	**

* Limit of non-inferiority for the primary efficacy variable (clinical/radiological response at test of cure) was prospectively defined as ≥-15%.
* Treatment differences and 95% CIs are not presented due to the small numbers of patients.

Bacteriological success rates at the test of cure visit for the PP and ITT populations in the supporting studies 551 and 592 are presented in the Table below, together with treatment differences and 95% CIs.

Table 4: Bacteriological Responses at Test of Cure: Supporting Studies 551 and 592

	Success Rate Augmentin XR 2000/125mg bd (10 days)	Treatment Difference
	% (n/N)	% (95% CI)*
Bacteriology ITT Population		
551	86.8 (290/334)	(82.6, 90.2)
592	87.2 (348/399)	(83.4, 90.3)
Bacteriology PP Population		
551	92.6 (276/298)	(88.9, 95.2)
592	95.7 (309/323)	(92.7, 97.5)

The following table provides an indication of pathogens eradicated or presumed eradicated during all of the above trials.

Table 5: Number (%) of initial pathogens eradicated or presumed eradicated at TOC (for all pathogens combined and key pathogens[a])

Studies Combined: 546, 547, 556, 557, 600, 550, 551, 592				
	Augmentin XR 2000/125mg bd		All Comparators Combined	
	n/N[b]	(%)	*n/N*[a]	(%)
Test of Cure	**N=1058**[c]		**N=141**[c]	
All Pathogens	**1134/1256**	(90.3)	**139/177**	(78.5)
S. pneumoniae	**400/420**	(95.2)	**49/57**	(86.0)
PRSP	40/41	(97.6)	4/5	(80.0)
Ery-resistant S. pneumoniae	63/68	(92.6)	7/8	(87.5)
H. influenzae	**258/291**	**(88.7)**	**31/36**	**(86.1)**
Beta-lactamase positive	46/49	(93.9)	3/3	(100.0)
Beta-lactamase negative	211/241	(87.6)	28/33	(84.8)
M. catarrhalis	**78/82**	**(95.1)**	**5/6**	**(83.3)**
Beta-lactamase positive	67/70	(95.7)	5/6	(83.3)
Beta-lactamase negative	11/12	(91.7)	-	
H. parainfluenzae	**53/64**	**(82.8)**	**11/14**	**(78.6)**
Beta-lactamase positive	3/3	(100.0)	1/1	(100.0)
Beta-lactamase negative	50/62	(80.6)	10/13	(76.9)
***S.aureus* (MSSA)**	**60/71**	**(84.5)**	**12/16**	**(75.0)**
Beta-lactamase positive	49/59	(83.1)	11/15	(73.3)
Beta-lactamase negative	11/12	(91.7)	1/1	(100.0)
K.pneumoniae	**20/24**	**(83.3)**	**4/5**	**(80.0)**

[a] Bacteriology PP population
[b] *n/N* = number of pathogens with a bacteriological outcome of eradicated or presumed eradicated /number of pathogens.
[c] N = number of patients in the Bacteriology PP TOC population.

Notes: Each pathogen is counted for patients with more than one type of pathogen at screening. If a patient had more than one isolate of a pathogen with susceptibility data, each of the isolates has been included in the table.
Ery-resistant = macrolide-resistant
>>>The pathogenic role of *H. parainfluenzae* in respiratory tract infections is not well defined.
S. aureus is a common contaminant in cultures of respiratory tract infections.<<<

MICROBIOLOGY

Like other penicillins, amoxycillin has a bactericidal effect on sensitive organisms during the stage of active multiplication. However, amoxycillin is susceptible to hydrolysis by β-lactamases and the addition of clavulanic acid in AUGMENTIN extends the antimicrobial spectrum of amoxycillin to include organisms normally resistant to amoxycillin due to β-lactamase production. Thus AUGMENTIN XR 1000/62.5, like other combinations of amoxycillin/clavulanic acid, possesses the distinctive properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor. AUGMENTIN XR 1000/62.5 is bactericidal to a wide range of organisms as listed in the table below.

Table 6 – Organisms susceptible to AUGMENTIN XR 1000/62.5

Susceptible aerobes gram-positive
Staphylococcus aureus (MSSA)# *
Staphylococcus epidermidis MSSE)#
Streptococcus pneumoniae (including PRSP & MRSP) *
Streptococcus pyogenes *
Viridans Group *Streptococcus* *
Susceptible anaerobes gram-positive
Peptostreptococcus anaerobius
Peptostreptococcus magnus
Peptostreptococcus micros
Susceptible aerobes gram-negative
Haemophilus influenzae# *
Haemophilus parainfluenzae# *
Klebsiella pneumoniae# *
Moraxella catarrhalis# *
Susceptible anaerobes gram-negative
Bacteroides fragilis#
Eikenella corrodens#
Fusobacterium nucleatum#
Porphyromonas sp.
Prevotella sp.

Some members of these species of bacteria produce β-lactamase, rendering them non-susceptible to amoxycillin alone.
* Bacteriological eradication shown in clinical studies

Table 7 – Acquired resistance data for amoxycillin/clavulanic acid in Australia according to NCCLS guidelines (M100-S10) for amoxycillin/clavulanic acid

		Percentage of Strains	
	Number of Pathogens (n)	Intermediate	Resistant
Streptococcus pneumoniae *	1020	0.3	0.1
Haemophilus influenzae #	303	0.0	0.3

*: - Data collected between March to November 1997.
#: - Data collected in 1999.

Table 8 – MIC Distribution for Sensitive/intermediate *S. pneumoniae* Isolates

MIC ≤ 1	1 > MIC < 2	MIC ≥ 2
96.8%	2.3%	0.9%

Table 9– Acquired resistance data for amoxycillin/clavulanic acid from other countries

Organisms	Number of Pathogens (n)	Percentage acquired resistance (%)
Sensitive aerobe gram positive		
Enterococcus faecalis	178	1.7
Staphylococcus aureus	955	2
Staphylococcus aureus (MSSA)	2,458	2
Coagulase negative staphylococci	158	7
Streptococcus agalactiae	96	1
Streptococcus pneumoniae	196	8.5
Streptococcus pneumoniae (Pen-S)	154	0
Streptococcus pyogenes	76	0
Streptococcus species	28	0
Sensitive aerobe gram negative		
Escherichia coli	946	5
Haemophilus influenzae	180	1.1
Haemophilus influenzae (BLN)	150	1.3
Haemophilus influenzae (BLP)	30	0
Klebsiella pneumoniae	355	1
Klebsiella oxytoca	1,540	9.6
Moraxella catarrhalis	46	0
Proteus sp.	128	5
Sensitive anaerobe		
Clostridium species	42	0
Clostridium difficile	27	0
Peptostreptococcus species	17	0
Bacteroides fragilis	98	5
Bacteroides fragilis group	163	7
Fusobacterium species	16	0
Intermediate aerobe gram negative		
Acinetobacter sp.	49	12
Resistant aerobe gram positive		
Staphylococcus aureus (MRSA)	147	59.2
Resistant aerobe gram negative		
Citrobacter sp.	84	56
Enterobacter sp.	181	86
Morganella sp.	39	97
Providencia sp.	14	79
Serratia sp.	61	89
S. maltophilia	57	96

The percent acquired resistance data provided in the above table has been collected from the following countries during the time period specified: US, 1996; Canada, 1993-1994; US/Canada, 1996-1997; France, 1994-1995; US, Arabia, 1994-1995; US, 1996-1997; US, 1991-1993; Belgium, 1993-1994; UK, Netherlands, 1989-1995.

Note: Resistance can vary from region to region and information on local resistance should be taken into account.

Table 10 - Organisms Against Which Amoxycillin/Clavulanic Acid Has *In Vitro* Activity (Their clinical significance is unknown)

Organisms	N	MIC 90 (µg/mL)
GRAM POSITIVE AEROBES:		
Enterococcus faecalis	185	1
Staphylococcus aureus	229	1
Staphylococcus aureus (MSSA)	95	1
Staphylococcus aureus (MRSA)	20	16
Staphylococcus epidermidis	134	4
Staphylococcus saprophyticus	20	1
Coagulase negative staphylococci	83	2
Streptococcus agalactiae	20	0.06
Streptococcus pneumoniae	1,476	2
Streptococcus pyogenes	764	0.12
Streptococcus viridans	20	0.5
GRAM NEGATIVE AEROBES:		
Escherichia coli	325	8
Haemophilus influenzae	2,268	2
Haemophilus influenzae (BLN)	691	1
Haemophilus influenzae (BLP)	271	2
Klebsiella pneumoniae	200	4
Klebsiella oxytoca	34	8
Moraxella catarrhalis	35	0.25
Neisseria gonorrheae	35	1
Neisseria meningitidis	10	0.06
Proteus mirabilis	49	2
Proteus vulgaris	11	8
GRAM POSITIVE ANAEROBES:		
Clostridium species	13	0.5
Clostridium perfringens	16	0.06
Clostridium difficile	21	2
Peptostreptococcus species	19	0.5
GRAM NEGATIVE ANAEROBES:		
Bacteroides fragilis	98	2
Bacteroides fragilis group	163	4
Fusobacterium species	23	0.125
GRAM NEGATIVE ANAEROBES		
Bacteroides fragilis	20	4
Bacteroides fragilis	19	2
Bacteroides fragilis	24	2
Bacteroides fragilis	176	1
Bacteroides thetaiotamicron	14	32
Bacteroides vulgarus	21	4
Other *Bacteroides* sp. of *B. fragilis* group	17	16
Bacteroides fragilis group	80	8
Non-*B. fragilis*	163	2
Prevotella sp	15	8
Prevotella, Porphyromonas and Bacteroides sp.	27	0.25
Fusobacterium sp.	23	0.125
Fusobacterium sp.	14	0.125

P. capillosus	10	1
P. bivia	15	2
P. disiens	13	0.25
GRAM NEGATIVE ANAEROBES		
Clostridium perfringens	16	0.06
Clostridium perfringens	10	0.12
Clostridium perfringens	10	0.25
Clostridium difficile	21	2
Clostridium difficile	10	1
Clostridium difficile	10	1
Propionibacterium sp.	11	0.06
Peptostreptococcus and *Ruminococcus* sp.	23	0.25
Peptostreptococci	19	0.25
Peptostreptococcus sp	14	1.0
Peptostreptococcus sp.	19	0.5

Note: Methicillin resistant strains are resistant to AUGMENTIN tablets.

Proteus vulgaris and Klebsiella species may not be susceptible to AUGMENTIN tablets at concentrations of amoxycillin and clavulanic acid achieved in the plasma. However at concentrations of amoxycillin and clavulanic acid achievable in the urine the majority of strains are susceptible.

Susceptibility Testing

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint - should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated, or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

INDICATIONS

AUGMENTIN XR 1000/62.5 is indicated for short-term treatment of bacterial infections at the following sites when caused by susceptible organisms in adults aged 16 and above.

- Respiratory Tract Infections, e.g. community-acquired pneumonia and acute bacterial sinusitis, typically caused *by Streptococcus pneumoniae* (including penicillin-resistant *S. pneumoniae* - PRSP*), Haemophilus influenzae*, Moraxella catarrhalis** and *Streptococcus pyogenes*.

(*Some members of these species of bacteria produce beta-lactamase, rendering them non-susceptible to amoxycillin alone).

AUGMENTIN XR 1000/62.5 has been shown to be effective against strains of *S.pneumoniae* with penicillin MICs $\leq 4\mu g/mL$.

A comprehensive list of susceptible organisms is provided in the Microbiology section.

The treatment of mixed infections caused by amoxycillin susceptible organisms and beta lactamase producing organisms susceptible to AUGMENTIN XR 1000/62.5 should not require the addition of another antibiotic due to the amoxycillin content of AUGMENTIN XR 1000/62.5.

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine their susceptibility to AUGMENTIN. However, when there is reason to believe an infection may involve any of the β-lactamase producing organisms listed above, therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies. Once these results are known, therapy should be adjusted if appropriate.

CONTRAINDICATIONS

A history of allergic reaction to β-lactams eg. penicillins or cephalosporins is a contraindication.

AUGMENTIN XR 1000/62.5 tablets are contraindicated in patients with a previous history of amoxycillin/clavulanic acid-associated jaundice or hepatic dysfunction.

PRECAUTIONS

Before initiating therapy with AUGMENTIN XR 1000/62.5, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins or cephalosporins.

Serious and occasionally fatal hypersensitivity (anaphylactic) 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 a 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 AUGMENTIN XR 1000/62.5 should be discontinued and the appropriate therapy instituted. Serious anaphylactic 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 amoxycillin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. 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). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases appropriate therapy with a suitable oral antibiotic agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, eg. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Since AUGMENTIN XR 1000/62.5 tablets contain amoxycillin, an aminopenicillin, these are 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 amoxycillin is used.

AUGMENTIN XR 1000/62.5 tablets should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxycillin induced skin rashes.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

The possibility of 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.

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

AUGMENTIN XR 1000/62.5 tablets should be used with care in patients with evidence of hepatic dysfunction. Hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins. Hepatic events subsequent to amoxycillin/ clavulanic acid have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

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 amoxycillin/clavulanic acid have occurred predominantly in males and elderly patients and may be associated with prolonged treatment.

AUGMENTIN XR 1000/62.5 tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 30mL/min).

The safety and efficacy of AUGMENTIN XR 1000/62.5 has not been established in patients below 16 ars of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

The genotoxic potential of amoxycillin/clavulanic acid was investigated in assays for chromosomal damage (mouse micronuclucleus test and a dominant lethal test) and gene conversion. All were negative.

Amoxycillin/clavulanic acid at oral doses of up to 1200 mg/kg/day had no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxycillin and clavulanate.

Use in Pregnancy: (Category B1).
Animal studies with orally and parenterally administered amoxycillin/clavulanic acid have shown no teratogenic effects. There is limited experience of the use of amoxycillin/clavulanic acid tablets in human pregnancy. In women with preterm, premature rupture of the foetal membrane (pPROM), prophylactic treatment with amoxycillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of AUGMENTIN TABLETS 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 obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation: Amoxycillin is excreted in the milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when AUGMENTIN XR 1000/62.5 tablets are administered to a nursing woman.

INTERACTIONS

Drug/Laboratory Test Interactions: Oral administration of AUGMENTIN XR 1000/62.5 tablets will result in high urine concentrations of amoxycillin. Since high urine concentrations of amoxycillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Testape®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with amoxycillin and therefore AUGMENTIN XR 1000/62.5 tablets.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxycillin but does not affect clavulanic acid excretion. Concurrent use with AUGMENTIN XR 1000/62.5 tablets may result in increased and prolonged blood levels of amoxycillin but not of clavulanic acid.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with AUGMENTIN XR 1000/62.5 tablets and allopurinol administered concurrently.

No information is available about the concurrent use of AUGMENTIN XR 1000/62.5 tablets and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram (Antabuse) like reaction in some patients. Therefore the ingestion of alcohol should be avoided during and for several days after treatment with AUGMENTIN XR 1000/62.5.

In common with other ~~broad-spectrum~~ antibiotics, AUGMENTIN XR 1000/62.5 tablets may ~~reduce~~ affect the gut flora, leading to lower oestrogen reabsorption and reduced ~~the~~ efficacy of combined oral contraceptives. ~~and patients should be warned accordingly~~.

ADVERSE REACTIONS

Clinical Trials

In the AUGMENTIN XR 1000/62.5 clinical study program the most frequently reported adverse experiences with a suspected or probable relationship to AUGMENTIN XR 1000/62.5 were: diarrhoea (17.0%), headache (3.7%), nausea (3.3%), and abdominal pain (2.4%).

The observed difference in the incidence of diarrhoea between AUGMENTIN XR 1000/62.5 tablets and currently available formulations of AUGMENTIN (14.8% vs 12.7%) was not statistically significant. The majority of patients reporting an AE of diarrhoea did so during the first 5 days of therapy.

The most frequently reported adverse events during clinical trials with AUGMENTIN XR 1000/62.5 are summarised in the table below. It should be noted that causality has not necessarily been established for these events:

Table 11. Percentage of patients with the frequently reported* adverse experiences in the "controlled studies" and "all exposed" populations, on therapy and 30 days post-therapy

	'ALL EXPOSED' (546, 547, 548, 549, 550, 551, 592, 556,557, 600)		'CONTROLLED STUDIES' (546, 548, 549, 550, 556, 557, 600)			
Preferred Term	**AUGMENTIN XR 2000/125mg bd N= 4466**		**AUGMENTIN XR 2000/125mg bd N= 1679**		**All Comparators N= 1698**	
	n	**(%)**	**n**	**(%)**	**N**	**(%)**
Patients with at least one AE	2082	(46.6)	840	(50.0)	842	(49.6)
Diarrhoea	757	(17.0)	306	(18.2)	175	(10.3)
Nausea	147	(3.3)	68	(4.1)	83	(4.9)
Headache	165	(3.7)	67	(4.0)	52	(3.1)
Abdominal pain	108	(2.4)	42	(2.5)	58	(3.4)
Vomiting	86	(1.9)	38	(2.3)	33	(1.9)
Genital Moniliasis	95	(2.1)	36	(2.1)	12	(0.7)
Rhinitis	65	(1.5)	32	(1.9)	38	(2.2)
Insomnia	71	(1.6)	29	(1.7)	34	(2.0)

**All Comparators were clarithromycin 500mg bd (n=295), levofloxacin 500mg od (n=497), Augmentin 875/125mg bd (n= 570), Augmentin 1000/125mg tds (n=175) and Augmentin 875/125 mg tds (n=161).
Studies 548 and 549 are two studies conducted in Acute Exacerbations of Chronic Bronchitis (AECB) and were included in the overall evaluation of safety

* ≥ 2% of patients in any treatment group.

Post Marketing

In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with AUGMENTIN XR 1000/62.5 tablets.

The following convention has been used for the classification of frequency:

very common	≥1/10
common	≥1/100 and <1/10
uncommon	≥1/1000 and <1/100
rare	≥1/10000 and <1/1000
very rare	<1/10000

Infections and Infestations

Common: mucocutaneous candidiasis

Gastro-intestinal

rare: nausea, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis. ~~Mucocutaneous candidiasis and~~ Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (See Precautions).

He[illegible]obiliary

ra[illegible] moderate rise in AST and/or ALT. Hepatitis, cholestatic jaundice which may be severe but is usually reversible. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

CNS

very rare: reversible hyperactivity, dizziness, headache, convulsions. Convulsions may occur in patients with impaired renal function or those receiving high doses.

Haematopoietic and lymphatic systems

rare: anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leukopenia (including neutropenia or agranulocytosis) these are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena, prolongation of bleeding time and prothrombin time.

Uncommon: thrombocytosis.

Hypersensitivity and skin

common: skin rashes, pruritis, urticaria

rare: angioneurotic oedema, anaphylaxis, serum-sickness-like syndrome, erythema multiforme, Stevens-Johnson syndrome, hypersensitivity, vasculitis, toxic epidermal necrolysis, bullous exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP) have been reported rarely. Whenever such reactions occur, AUGMENTIN XR 1000/62.5 should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use of AUGMENTIN XR 1000/62.5 is considered essential. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillins (See Precautions).

Miscellaneous

rare: interstitial nephritis, crystalluria, superficial tooth discolouration which can usually be removed by brushing.

DOSAGE AND ADMINISTRATION

AUGMENTIN XR 1000/62.5 tablets **should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.** For the

convenience of the patient, the tablets may be broken in half, provided that the two halves are taken on the same occasion.

AUGMENTIN XR 1000/62.5 is indicated for use in adults 16 years of age and above.

Adults:

2 tablets every 12 hours for a minimum of 7 days.

Treatment should be continued for 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. Efficacy in acute bacterial sinusitis is based on a 10 day treatment duration (See Indications).

Treatment should not be extended beyond 14 days without review. Due to differences in the pharmacokinetic profile of AUGMENTIN XR 1000/62.5 tablets, 2 AUGMENTIN XR 1000/62.5 tablets are NOT bioequivalent to other combinations of AUGMENTIN and/or AMOXIL tablets such as 1 AUGMENTIN DUO 500/125mg tablet and 3 AMOXIL 500mg capsules.

Adults with Impaired Renal Function:
No adjustment in dosage is required in patients with creatinine clearance >/= 30 mL/min.

AUGMENTIN XR 1000/62.5 is not recommended in patients with creatinine clearance < 30 ml/min.

Both amoxycillin and clavulanic acid are excreted by the kidneys and the serum half life of each increases in patients with renal failure

AUGMENTIN XR 1000/62.5 is not recommended in haemodialysis patients.

Adults with Impaired Hepatic Function:
Data is currently insufficient for a dosage recommendation. Dose with caution, and monitor hepatic function at regular intervals.

Elderly
No adjustment needed.

Children
Safety and effectiveness in paediatric patients below the age of 16 years have not been established. Patients below the age of 16 years, should be dosed with the alternative AUGMENTIN formulations in usual doses of 20mg/kg/day based on amoxycillin content.

OVERDOSAGE

Se ıs and severe clinical symptoms are unlikely to occur after overdosage with AUGMENTIN XR 10 62.5 tablets. If encountered, gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxycillin may be removed from the circulation by haemodialysis.

Amoxycillin crystalluria has been observed

STORAGE

AUGMENTIN XR 1000/62.5 tablets should be stored below 25°C and protected from moisture. Under these conditions the shelf life is 24 months.

PRESENTATIONS

AUGMENTIN XR 1000/62.5 Tablets are white, capsule shaped, film coated tablets debossed with "AC 1000/62.5" on one side and a bisect breakline on the other. Each tablet has an immediate layer containing 562.5mg amoxycillin as the trihydrate and 62.5mg clavulanic acid as the potassium salt, and a sustained release layer containing 437.5mg amoxycillin as the sodium salt. Available as blister packs of 28 or 40 tablets.

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