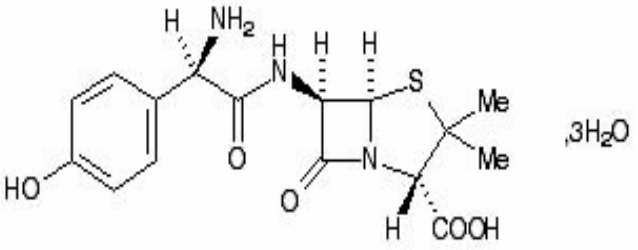
AUGMENTIN® DUO and AUGMENTIN® DUO FORTE TABLETS
PRODUCT INFORMATION
(Amoxycillin Trihydrate and Potassium Clavulanate)

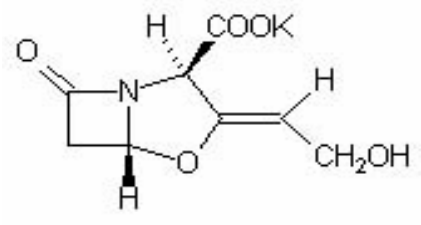
DESCRIPTION

AUGMENTIN DUO and AUGMENTIN DUO FORTE tablets (AUGMENTIN TABLETS) are combination products containing the semisynthetic antibiotic, amoxycillin (as the trihydrate) and the
β-lactamase inhibitor, potassium clavulanate (as the potassium salt of clavulanic acid). 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.

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 DUO FORTE TABLETS also contain the inactive ingredients: magnesium stearate, sodium starch glycollate, silica - colloidal anhydrous and microcrystalline cellulose. The tablet coating contains titanium dioxide, hypromellose 5 & 15 cps, Macrogol 4000 & Macrogol 6000.
AUGMENTIN DUO TABLETS also contain the inactive ingredients: magnesium stearate, sodium starch glycollate, silica - colloidal anhydrous and microcrystalline cellulose. The tablet coating contains titanium dioxide, hypromellose 15cps, propylene glycol, ethylcellulose and dimethicone 200.

PHARMACOLOGY

Pharmacokinetics

Absorption

AUGMENTIN TABLETS are stable in the presence of gastric acid. Their two components are rapidly absorbed if administered 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 TABLETS should be administered at the start of a meal. The pharmacokinetics of amoxycillin are not affected by food.

Oral administration of AUGMENTIN DUO FORTE (875mg/125mg) tablets every 12 hours was compared with AUGMENTIN FORTE (500mg/125mg) every 8 hours at the start of a light meal. The following mean pharmacokinetic parameters were observed for amoxycillin for AUGMENTIN DUO FORTE (875/125mg) taken every 12 hours and AUGMENTIN FORTE (500mg/125mg) taken every 8 hours respectively: peak plasma concentration (C_{max}) of 11.64 and 7.19 µg/mL, area under the plasma concentration-time curve between 0 and 24 hours after the first dose ($AUC_{(0\text{-}24\ hours)}$) of 53.52 and 53.35 µg.h/mL, half life (t½) of 1.19 and 1.15 hours, time to peak plasma concentration (T_{max}) of 1.50 and 1.50 hours and the time above the minimum inhibitory concentration (T_{MIC} 24 hours) of 10.46 hours and 13.30 hours.

The following pharmacokinetic parameters were observed for clavulanic acid for AUGMENTIN DUO FORTE (875/125mg) tablets taken every 12 hours and AUGMENTIN FORTE (500mg/125mg) taken every 8 hours respectively: C_{max} of 2.18 and 2.40 µg /mL, $AUC_{(0\text{-}24\ hours)}$ of 10.16 and 15.72 µg.h/mL, t½ of 0.96 and 0.98 hours and T_{max} of 1.25 and 1.50 hours, and (T_{MIC} 24 hours) of 6.08 hours and 9.43 hours.

The t½ and C_{max} for clavulanate for AUGMENTIN DUO FORTE were not significantly different from AUGMENTIN FORTE. However, the $AUC_{(0\text{-}24\ hours)}$ was reduced, as would be expected with the lower daily dose of clavulanate ie 250mg in AUGMENTIN DUO FORTE vs 375mg in AUGMENTIN FORTE

Oral administration of AUGMENTIN DUO (500mg/125mg) every 12 hours was compared with AUGMENTIN (250mg/125mg) every 8 hours at the start of a light meal.

The following mean pharmacokinetic parameters were observed for amoxycillin for AUGMENTIN DUO (500/125mg) taken every 12 hours and AUGMENTIN (250mg/125mg) taken every 8 hours respectively: peak plasma concentration (Cmax) of 6.51 and 3.32 µg/mL, area under the plasma concentration-time curve between 0 and 24 hours after the first dose (AUC(0-24 hours)) of 33.43 and 26.66 µg.h/mL, half life (t½) of 1.26 and 1.36 hours, time to peak plasma concentration (Tmax)

of 1.50 and 1.50 hours and the time above the minimum inhibitory concentration (TMIC 24 hours) of 8.54 hours and 9.49 hours.

The following pharmacokinetic parameters were observed for clavulanic acid for AUGMENTIN DUO (500/125mg) taken every tablets every 12 hours and AUGMENTIN (250mg/125mg) taken every 8 hours respectively: Cmax of 1.75 and 1.47 µg/mL, AUC(0-24 hours) of 8.6 and 12.6 µg.h/mL, t½ of 1.01 and 1.01 hours and Tmax of 1.50 and 1.50 hours, and (TMIC 24 hours) of 5.69 hours and 8.24 hours.

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 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. Clavulanic acid has been variously reported to be bound to human serum in the range of 9 - 30% and amoxycillin approximately 20% bound. 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 radiolabelled 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

AUGMENTIN DUO FORTE vs AUGMENTIN FORTE

Three pivotal studies in 1,361 patients treated for between 7 and 14 days for either lower respiratory tract infections, upper respiratory infections or complicated urinary tract infections compared a regimen of AUGMENTIN DUO FORTE (875/125 mg) tablets every 12 hours (q12h) to AUGMENTIN FORTE (500/125 mg) tablets dosed every 8 hours (q8h) (584, 170 and 607 patients, respectively). Comparable efficacy was demonstrated between the q12h and q8h dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most frequently reported adverse event in two of the studies was diarrhoea; incidence rates were similar for the 875/125 mg q12h and 500/125 mg q8h dosing regimens (14.9% and 14.3%, respectively). However, there was a statistically significant difference ($p<0.05$) in rates of severe diarrhoea or withdrawals with diarrhoea between the regimens: 1.0% for 875/125 mg q12h dosing versus 2.5% for the 500/125 mg q8h dosing. In the third study the most frequently reported adverse event was headache with an incidence of 5.7% (AUGMENTIN FORTE q8h) vs 8.3% (AUGMENTIN DUO FORTE q12h).

As noted previously although there was no significant difference in the percentage of adverse events in each group there was a statistically significant difference in rates of severe diarrhoea or withdrawals with diarrhoea between the regimens.

AUGMENTIN DUO vs AUGMENTIN

Two pivotal studies in 908 patients treated for between 5 and 10 days for either uncomplicated Skin and Skin Structure Infections or Acute Exacerbation of Chronic Bronchitis compared a regimen of AUGMENTIN DUO (500/125mg) tablets every 12 hours with AUGMENTIN (250/125mg) tablets every 8 hours. Comparable efficacy was demonstrated between the 12 hourly and 8 hourly dosing regimens.

There was no significant difference in the percentage of adverse events in each group, with the most frequently reported adverse event in the two studies being diarrhoea.

The clinical efficacy of AUGMENTIN tablets given in a twice daily versus three times daily regimen have been shown to be comparable in AECB and SSSI, despite the differences in some pharmacokinetic parameters.

Given the similar TMIC and the demonstration of equivalence between AECB and SSSI it would be reasonable to extrapolate to the remaining indications. Clinical safety and efficacy in other indications were investigated, however these supportive studies were not sufficiently designed to demonstrate the relative efficacy of the two Augmentin regimens, or compared the proposed regimen with other treatments.

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 TABLETS extends the antimicrobial spectrum of amoxycillin to include organisms normally resistant to amoxycillin due to β-lactamase production. *In vitro* studies have demonstrated the susceptibility of most strains of the following organisms:

Table 1 – 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 2 – MIC Distribution for Sensitive/intermediate *S. pneumoniae* Isolates

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

Table 3– Acquired resistance data for amoxycillin/clavulanic acid from other countries

Breakpoints	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 4- MIC Interpretive Standards (µg/mL) according to NCCLS guidelines (M100-S10) for amoxycillin and amoxycillin/clavulanic acid

Organisms	Antimicrobial Agents	MIC (µg/mL) Interpretive Standards		
		S	I	R
Enterobacteriaceae	amoxycillin/clavulanic acid	≤ 8/4	16/8	≥ 32/16
Non-Enterobacteriaceae*	NA	-	-	-
Staphylococcus sp.	amoxycillin/clavulanic acid	≤ 4/2	-	≥ 8/4
Enterococcus sp.*	NA	-	-	-
Haemophilus sp.	amoxycillin/clavulanic acid	≤ 4/2	-	≥ 8/4
Streptococcus pneumoniae	amoxycillin amoxycillin/clavulanic acid	≤ 2 ≤ 2/1	4 4/2	≥ 8 ≥ 8/4
Streptococcus sp. other than *S. pneumoniae***	NA	-	-	-

*No interpretive standards for amoxycillin or amoxycillin/clavulanic acid.
**A streptococcal isolate that is susceptible to penicillin can be considered susceptible to ampicillin, amoxycillin and amoxycillin/clavulanic acid.
The MIC90 data provided in the above table has been collected from the following countries during the time period specified: US: 91-97; UK: Not Stated; France: 94 – 95; Belgium: 93 – 94.
It should be noted that NCCLS breakpoints are reviewed on a regular basis and may be amended according to the data available.

The following in vitro data are available but their clinical significance is unknown.

Table 5- In Vitro Activity of amoxycillin/clavulanic acid

	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 vulgatus	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
B. 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

Diffusion Technique

For Kirby-Bauer method of susceptibility testing, a 30 mcg AUGMENTIN (20 mcg amoxycillin + 10 mcg clavulanic acid) diffusion disc should be used. With this procedure, a report from the

laboratory of "Susceptible" indicates that the infecting organism is likely to respond to AUGMENTIN therapy and a report of "Resistant" indicates that the infecting organism is not likely to respond to therapy. An "Intermediate Susceptibility" report suggests that the infecting organism would be susceptible to AUGMENTIN if the infection is confined to tissues or fluids (e.g. urine) in which high antibiotic levels are attained.

Dilution Techniques

Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) value susceptibility of bacterial isolates to AUGMENTIN. Tubes should be inoculated to contain 104 to 105 organisms/mL or plates "spotted" with 103 to 104 organisms.

The recommended dilution method employs a constant amoxycillin/ clavulanic acid ratio of 2 to 1 in all tubes with increasing concentrations of amoxycillin. MICs are reported in terms of amoxycillin concentration in the presence of clavulanic acid at constant 2 parts amoxycillin to 1 part clavulanic acid.

Recommended AUGMENTIN Susceptibility Ranges[1,2].

ORGANISMS	RESISTANT	INTERMEDIATE	SUSCEPTIBLE
Gram Negative Enteric Bacteria	≤13mm	14-17mm	≥18mm
Staphylococcus[3] and Haemophilus spp	≤19mm	-------	≥20mm

1. The non-β-lactamase-producing organisms which are normally susceptible to ampicillin, such as Streptococci, will have similar zone sizes as for ampicillin discs.

2. The quality control cultures should have the following assigned daily ranges for AUGMENTIN:

	Discs	Mode MIC (mg/L)
E. coli (ATCC25922)	19-25mm	4/2 - 8/4
S. aureus (ATCC25923)	28-36mm	0.25/0.12 - 0.5/0.25
E. coli (ATCC35218)	18-22mm	4/2 - 8/4

The Mode MIC is expressed as the concentration of amoxycillin/clavulanic acid.

3. Organisms which show susceptibility to AUGMENTIN but are resistant to methicillin/oxacillin should be considered resistant.

INDICATIONS

AUGMENTIN TABLETS are indicated for short term treatment of bacterial infections at the following sites when caused by sensitive organisms (refer to Microbiology):

Urinary Tract Infections (uncomplicated and complicated)

Lower Respiratory Tract Infections, including community acquired pneumonia and acute exacerbations of chronic bronchitis

Upper Respiratory Tract Infections, such as sinusitis, otitis media and recurrent tonsillitis.

Skin and Skin Structure Infection

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to AUGMENTIN TABLETS. 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.

The treatment of mixed infections caused by amoxycillin susceptible organisms and β-lactamase producing organisms susceptible to AUGMENTIN TABLETS should not require the addition of another antibiotic due to the amoxycillin content of these products.

CONTRAINDICATIONS

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

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

WARNINGS

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 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 DUO FORTE 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 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.

PRECAUTIONS

General:

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

Since AUGMENTIN 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 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.

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 AUGMENTIN have occurred predominantly in males and elderly patients and may be associated with prolonged treatment.

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

AUGMENTIN DUO FORTE tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 30mL/min).
AUGMENTIN DUO tablets should be used with care in patients with moderate or severe renal impairment. The dosage of AUGMENTIN DUO should be adjusted as recommended in the "DOSAGE AND ADMINISTRATION" section

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

Use in Pregnancy: (Category B1). Animal studies with orally and parenterally administered AUGMENTIN have shown no teratogenic effects. There is limited experience of the use of AUGMENTIN TABLETS in human pregnancy. In women with preterm, premature rupture of the foetal mebrane (pPROM), prophylactic treatment with AUGMENTIN 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 TABLETS are administered to a nursing woman.

INTERACTIONS

Drug/Laboratory Test Interactions: Oral administration of AUGMENTIN TABLETS will result in high urine concentrations of amoxycillin. Since high urine concentrations of ampicillin 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 TABLETS.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxycillin but does not affect clavulanic acid excretion. Concurrent use with AUGMENTIN 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 TABLETS and allopurinol administered concurrently.

No information is available about the concurrent use of AUGMENTIN 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 DUO FORTE.

In common with other antibiotics, AUGMENTIN TABLETS may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

ADVERSE REACTIONS

AUGMENTIN is generally well tolerated. The majority of events were of a mild and transient nature.

Clinical Trials

During clinical trials, the most frequently reported adverse events related or possibly related to AUGMENTIN DUO FORTE therapy were diarrhoea (14.9%), nausea (7.9%), headache (6.8%), abdominal pain (4.5%), vomiting (3.8%), genital moniliasis (3.6%) and vaginitis (3.4%).

The following adverse events have been observed during clinical trials with AUGMENTIN DUO FORTE, however it should be noted that causality has not necessarily been established for these events:

The most frequently (≥ 1%) reported adverse experiences in decreasing order for the BD regimen

875/125mg q 12hr

Total Number of Patients	**584**
Adverse Event	**Frequency (%)**
Diarrhoea #	14.9
Nausea	7.9
Headache	6.8
Abdominal pain	4.5
Vomiting	3.8
Genital moniliasis	3.6
Vaginitis	3.4*
Back Pain	1.9
Dizziness	1.7
Fungal infection	1.7
Rash	1.5
Sinusitis	1.4
Fatigue	1.2
Genital pruritus	1.2
Injury	1.0
Pain	1.0
Urinary tract infection	1.0
Insomnia	1.0
Myalgia	1.0

During clinical trials, the most frequently reported adverse events related or possibly related to AUGMENTIN DUO therapy were diarrhoea (12.8%), nausea (5.2%), headache (4.8%), abdominal pain (4.5%).

The following adverse events have been observed during clinical trials with AUGMENTIN DUO, however it should be noted that causality has not necessarily been established for these events:

The most frequently (≥ 1%) reported adverse experiences in decreasing order for the BD regimen

	500/125mg q 12hr
Total Number of Patients	**462**
Adverse Event	**Frequency (%)**
Diarrhoea	12.8
Nausea	5.2
Headache	4.8
Upper Respiratory Infection	1.9
Genital moniliasis	1.9
Vomiting	1.5

Dyspepsia	1.1
Injury	1.1

Post Marketing

In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with AUGMENTIN DUO and DUO FORTE tablets:

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. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), See Warnings.

Hepatobiliary *rare*: moderate rise in AST and/or ALT. Hepatitis, cholestatic jaundice which may be severe but is usually reversible.

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 dermatitis and acute generalised exanthematous putulosis (AGEP) have been reported rarely. Whenever such reactions occur, AUGMENTIN DUO should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use of AUGMENTIN DUO is considered essential. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillins (See Warnings).

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

DOSAGE AND ADMINISTRATION

AUGMENTIN TABLETS **should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.**

Adults:

The usual adult dose is one AUGMENTIN DUO tablet every 12 hours. For more severe infections, the dose should be one AUGMENTIN DUO FORTE tablet every 12 hours.

Note: Since both AUGMENTIN DUO FORTE and AUGMENTIN DUO tablets contain the same amount of clavulanic acid (125mg, as the potassium salt), two AUGMENTIN DUO tablets are not equivalent to one AUGMENTIN DUO FORTE tablet. Therefore, two AUGMENTIN DUO tablets should not be substituted for one AUGMENTIN DUO FORTE tablet for treatment of more severe infections.

Treatment should usually be continued for 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. Treatment should not exceed 14 days without review.

Adults with Impaired Renal Function:

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

Both amoxycillin and clavulanic acid are excreted by the kidneys and the serum half life of each increases in patients with renal failure. *No adjustment to the initial AUGMENTIN dose is necessary, but the dosing interval should be extended according to the degree of renal impairment.

The following schedule is proposed for AUGMENTIN DUO:

Mild Impairment: (Creatinine clearance > 30mL/min)	No change in dosage.
Moderate Impairment: (Creatinine clearance 10 - 30mL/min)	One AUGMENTIN DUO tablet 12 hourly
Severe Impairment: (Creatinine clearance < 10mL/min)	One AUGMENTIN DUO tablet every 24 hours

Haemodialysis decreases serum concentrations of both amoxycillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Adults with Impaired Hepatic Function:

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

Children

Children weighing 40 Kg and more should be dosed according to the adult recommendations.

It is recommended that AUGMENTIN suspensions be used for children weighing less than 40 kg.

OVERDOSAGE

Serious and severe clinical symptoms are unlikely to occur after overdosage with AUGMENTIN 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.

STORAGE

AUGMENTIN TABLETS should be stored below 25^{o}C and protected from moisture. Under these conditions the shelf life is 18 months.

PRESENTATIONS

AUGMENTIN DUO FORTE Tablets: Each film coated tablet contains 875mg amoxycillin as the trihydrate and 125mg clavulanic acid as the potassium salt. Available as blister packs of 10.

AUGMENTIN DUO Tablets: Each film coated tablet contains 500mg amoxycillin as the trihydrate and 125mg clavulanic acid as the potassium salt. Available as blister packs of 10.

SPONSOR

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