FLEMING

Fleming Oral Suspension 228.5mg/ 5mL
Fleming Oral Suspension 457mg/ 5mL

Product Description

Fleming Oral Suspension 228.5mg/ 5mL: An off white, free flowing powder, which on reconstitution becomes an off-white suspension having a characteristic odour. Each 5mL contains 200mg of amoxicillin and 28.5mg of clavulanic acid.

Fleming Oral Suspension 457mg/ 5mL: An off white free flowing powder, which on reconstitution becomes an off-white suspension having a characteristic odour. Each 5mL contains 400mg of amoxicillin and 57mg of clavulanic acid.

When reconstituted, an off-white suspension is formed.

Fleming oral presentations do not contain sucrose, tartrazine or any other azo dyes.

The amoxicillin is present as amoxicillin trihydrate and the clavulanic acid is present as potassium clavulanate. The oral suspension presentations are dry powder oral suspensions for reconstitution in water, at the time of dispensing, to form an oral sugar free oral suspension.

Pharmacodynamics

Fleming is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital.
The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen.

The clavulanate in Fleming anticipates this defence mechanism by blocking the β-lactamase enzymes, thus rendering the organisms sensitive to amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body.

Clavulanate by itself has little antibacterial activity; however, in association with amoxicillin as Fleming, it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

Microbiology: Fleming is bactericidal to a wide range of organisms including:

Gram-positive: Aerobes: **Enterococcus faecalis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, *Staphylococcus aureus, *Coagulase-negative staphylococci (including Staphylococcus epidermidis), Corynebacterium sp, *Bacillus anthracis, Listeria monocytogenes, Enterococcus faecium, Streptococcus agalactiae, Streptococcus sp.*

Anaerobes: *Clostridium, Peptococcus spp, Peptostreptococcus.*

Gram-negative: Aerobes: **Haemophilus influenzae, *Escherichia coli, *Proteus mirabilis, *Proteus vulgaris, *Klebsiella sp, *Moraxella catarrhalis (Branhamella catharralis), *Salmonella sp, *Shigella sp, Bordetella pertussis, Brucella sp, *Neisseria gonorrhoeae, *Neisseria meningitidis, Vibrio cholerae, *Yersinia enterocolitica, Pasteurella multocida. Gardnerella vaginalis, Helicobacter pylori, Legionella sp.*

Anaerobes: **Bacteroides sp (*including *Bacteroides fragilis), *Fusobacterium sp.*

*Including β-lactamase producing strains resistant to ampicillin and amoxicillin.

Infections caused by amoxicillin-susceptible organisms are amenable to Fleming treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Fleming-susceptible β-lactamase-producing organisms may therefore be treated with Fleming.

Pharmacokinetics

Peak serum levels of both occur about 1 hr after oral administration. Absorption of Fleming is optimised at the start of a meal.

The pharmacokinetics of the 2 components of Fleming are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Doubling the dosage of Fleming approximately doubles the serum levels achieved.

Pharmacokinetic studies have been performed in children, to compare Fleming thrice daily and twice daily. All of these data indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

The mean AUC values for amoxicillin are essentially the same following twice a day dosing with the Fleming 875/125-mg tab or 3 times a day dosing with the Fleming 500/125-mg tab, in adults. No differences between the 875 mg twice daily and 500 mg thrice daily dosing regimens are seen when comparing the amoxicillin $T_{1/2}$ or C_{max}, after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

The time of dosing of Fleming relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the Fleming 875/125-mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and C_{max}, the highest mean values and smallest intersubject variabilities were achieved by administering Fleming at the start of a meal, compared to the fasting state or 30 or 150 min after the start of a meal.

Title: Art Work Approval Form			
MEDREICH LIMITED		Specification:	Printed on 40 - 45 GSM news print paper.
Product	Fleming Susp 228.5mg-457mg - S/L - Eng - PIL		
Customer	Healol - Malaysia	Colours:	2 - Red 032 C and Black
Reason for Issue	AWR No.: 1000AW2010391/392 (Old Artwork: 1218171) a) Artwork revision to remove Medreich PLC name & address	Dimensions:	195 x 300 mm (Open Size) 190 x 38 mm (Folded size)
Related FG Codes	1300460 / 1304567 / Pharmacode No. 4707	No. of Folds (only for PIL)	3 / Artwork made to 70%
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HEA/FLE/PIL/02
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The mean C_{max}, T_{max}, $T_{1/2}$ and AUC values for amoxicillin and clavulanic acid are given as follows for an 875 mg/125 mg dose of amoxicillin/clavulanic acid administered at the start of a meal. (See Table 1.)

Table 1 – Mean Pharmacokinetic Parameters

Drug Administration	Dose (mg)	C_{max} (mg/L)	T_{max}* (hrs)	AUC (mg.hr/L)	$T_{1/2}$ (hrs)
Fleming 1 g Amoxicillin Clavulanic acid	875 125	12.4 3.3	1.5 1.3	29.90 6.88	1.36 0.92

* Median values

Amoxicillin serum concentrations achieved with Fleming are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution: The pharmacokinetics of the 2 components of Fleming are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Doubling the dosage of Fleming approximately doubles the serum levels achieved.

Indication

Fleming is indicated for short-term treatment of bacterial infections at the following sites:

Upper respiratory tract infections (including ENT), e.g. tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections, e.g. acute and acute exacerbations of chronic bronchitis, lobar and bronchopneumonia.

Genito-urinary tract infections, e.g. cystitis, urethritis, pyelonephritis.

Skin and soft tissue infections, e.g. boils, abscesses, cellulitis, wound infections.

Bone and joint infections, e.g. osteomyelitis.

Dental infections, e.g. dento-alveolar abscess

Other infections, e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis.

Recommended Dose

Children

The usual recommended daily dosage is expressed as amoxicillin/ clavulanic acid

- **25/3.6mg/ kg/day** in mild to moderate infections (upper respiratory tract infections e.g., recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections)
- **45/6.4mg/ kg/day** for the treatment of more serious infections (upper respiratory tract infections e.g., otitis media and sinusitis, lower respiratory tract infections e.g. bronchopneumonia and urinary tract infections)

Tables 2 and 3 below give dosage guidelines for children.

Children > 2 years: See Table 2

Table 2

Usual Recommended Daily Dosage	**Age (weight)**	**Dosage**	
		Fleming Oral Suspension 228.5mg/ 5mL	**Fleming Oral Suspension 457mg/ 5mL**
Mild to moderate infections (25/3.6mg/ kg/day)	2 – 6 years (13 – 21 kg)	5 mL	2.5 mL
	7 – 12 years (22 – 40 kg)	10 mL	5 mL
More serious infections (45/6.4mg/ kg/day)	2 – 6 years (13 – 21 kg)	10 mL	5 mL
	7 – 12 years (22 – 40 kg)	20 mL	10 mL

Children 2 months to 2 years: See Table 3. Children < 2 years should be dosed according to body weight

Table 3

Weight (kg)	Dosage			
	Fleming Oral Suspension 228.5mg/ 5mL		Fleming Oral Suspension 457mg/ 5mL	
	Mild to moderate infections	More serious infections	Mild to moderate infections	More serious infections
	25/3.6mg/ kg/day (mL per dose twice daily)	45/6.4mg/ kg/day (mL per dose twice daily)	25/3.6mg/ kg/day (mL per dose twice daily)	45/6.4mg/ kg/day (mL per dose twice daily)
2	0.6	1.2	0.3	0.6
3	1.0	1.6	0.5	0.8
4	1.2	2.2	0.6	1.1
5	1.6	2.8	0.8	1.4
6	1.8	3.4	0.9	1.7
7	2.2	4.0	1.1	2.0
8	2.6	4.6	1.3	2.3
9	2.8	5.0	1.4	2.5
10	3.2	5.6	1.6	2.8
11	3.4	6.2	1.7	3.1
12	3.8	6.8	1.9	3.4
13	4.0	7.4	2.0	3.7
14	4.4	7.8	2.2	3.9
15	4.6	8.4	2.3	4.2

There is insufficient experience with Fleming Oral preparations to make dosage recommendations for children under 2 months old.

Renal Impairment

For very young children with immature renal function Fleming Oral Suspension is not recommended.

For children with a GFR of <30 mL/min Fleming Oral Suspension is not recommended.

For children with a GFR of >30 mL/min, no adjustment in dosage is required.

Hepatic Impairment

Dose with caution; monitor hepatic function at regular intervals.

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of Fleming is optimised when taken at the start of a meal.

Therapy can be started parenterally and continued with an oral preparation.

Treatment should not be extended beyond 14 days without review.

Duration of therapy should be appropriate to the indication.

Route of Administration

Oral

Contraindications

Penicillin hypersensitivity.

Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g., cephalosporins.

A previous history of co-amoxiclav or penicillin-associated jaundice/hepatic dysfunction.

Warnings and Precautions

Changes in liver function tests have been observed in some patients receiving amoxicillin + clavulanic acid. The clinical significance of these changes is uncertain but amoxicillin + clavulanic acid should be used with caution in patients with evidence of hepatic dysfunction. Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

Not to be used in patients with known hypersensitivity to penicillin.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Fleming, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Fleming must be discontinued immediately and appropriate alternative therapy instituted.

Erythematous rashes have been associated with glandular fever in patients receiving amoxicillin. Fleming should be avoided if glandular fever is suspected.

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

Fleming Oral Suspension contains aspartame. It is unsuitable for phenylketonurics.

Interactions with Other Medicaments

Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Co-amoxiclav should be used with care in patients on anti-coagulation therapy. In common with other broad-spectrum antibiotics, co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin.

Concomitant use with co-amoxiclav may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol.

Pregnancy and Lactation

There is limited experience of the use of co-amoxiclav in human pregnancy. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician. Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the infant.

Side Effects

Side effects, as with amoxicillin, are uncommon and mainly of a mild and transitory nature.

Gastrointestinal reactions

Effects include diarrhoea, indigestion, nausea and vomiting. Candidiasis, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) have been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking Fleming at the start of meals. As with other antibiotics the incidence of gastrointestinal side effects may be raised in children under 2 years. In clinical trials, however, only 4% of children under 2 years were withdrawn from treatment.

Hepatic effects

A moderate rise in AST and/or ALT has been noted in patients with semi-synthetic penicillins but the significance of these findings is unknown. Hepatitis and cholestatic jaundice have been reported rarely with co-amoxiclav. They may however be severe and continue for several months. They are reported as occurring predominantly in adult or elderly patients and slightly more frequently in males. Signs and symptoms may occur during treatment but are more frequently reported after cessation of therapy with a delay of up to six weeks. The hepatic events are usually reversible. However, in extremely rare circumstances, deaths have been reported. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

MEDREICH LIMITED — **Title: Art Work Approval Form**

Product	**Fleming Susp 228.5mg-457mg - S/L - Eng - PIL**	Specification:	**Printed on 40 - 45 GSM news print paper.**
Customer	**Healol - Malaysia**		
Reason for Issue	**AWR No.: 1000AW2010391/392** (Old Artwork: 1218171) a) Artwork revision to remove Medreich PLC name & address	Colours:	**2 - Red 032 C and Black**
		Dimensions:	**195 x 300 mm (Open Size) 190 x 38 mm (Folded size)**
Related FG Codes	**1300460 / 1304567** — Pharmacode No. **4707**	No. of Folds (only for PIL)	**3** — Artwork made to **70%**
Item Code	**1222461-V1 (WA)** — Layout No.: **NA**		
Verified By		Approved By	
PDC:	**PDC:**	**Regulatory:**	**QC:** **CQA:**

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Hypersensitivity reactions

Urticarial and erythematous rashes sometimes occur. Rarely erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis have been reported. Treatment should be discontinued if one of these types of rash appears.

In common with other β-lactam antibiotics angioedema, oedema, anaphylaxis serum sickness-like syndrome and hypersensitivity vasculitis have been reported.

Interstitial nephritis can occur rarely.

Haematological effects

As with other β-lactams, reversible leucopenia (including neutropenia or agranulocytosis) reversible thrombocytopenia and haemolytic anaemia have been reported rarely.

CNS effects

CNS effects have been seen very rarely. These include reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

Skin and Subcutaneous Tissue Disorders

Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Symptoms and Treatment of Overdose

Cases of overdosage with Fleming are unlikely to occur; 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. Co-amoxiclav may be removed from the circulation by haemodialysis.

Effects on Ability to Drive and Use Machine

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section Side Effects).

Instructions for Use

At time of dispensing, the dry powder should be reconstituted to form an oral suspension.

To reconstitute:

1. Tap the bottle gently to loosen the dry powder.

2. Add half the required amount of water and shake vigorously with the application of rubber stopper and cap.

3. Slowly add water up to the mark on the bottle (transparent circular raised-ring on body of bottle) and shake well with the application of rubber stopper and cap.

When first reconstituted, allow to stand for 5 minutes to ensure full dispersion.

Storage Condition

The dry powder should be stored below 30°C in unopened containers in a dry place. Reconstituted suspensions should be stored in a refrigerator (2-8°C) and used within 7 days.

Keep out of reach of children. Jauhkan daripada capaian kanak-kanak.

Shelf Life

24 months

ATC Code

J01CR02

Nature and Contents of Container

Glass bottle of 70mL. The oral suspension is supplied in 100ml Flint glass bottle plugged with Bromo butyl rubber stopper and capped with White PP screw cap with T/E red.

MAL Number

Fleming Oral Suspension 228.5mg/ 5mL: BRU20032798P / MAL06061693AZ

Fleming Oral Suspension 457mg/ 5mL: BRU20022777P / MAL09062129AZ

Date of Revision of Package Insert

November 2020

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