SCHEDULING STATUS: S4

1. NAME OF THE MEDICINAL PRODUCT
ACTIMENTIN 1000 (Amoxicillin/Clavulanic acid 875 mg/125 mg, Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.
Excipient with known effect: Each tablet contains 2.4 mg sodium.

3. PHARMACEUTICAL FORM
Film-coated tablets.
White to off white 22 mm by 10 mm oblong film-coated tablets with score line.
The score line is not intended for breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
ACTIMENTIN 1000 is indicated in adults for the treatment of the following infections caused by amoxicillin-clavulanate resistant organisms producing β-lactamases sensitive to clavulanic acid (see section 4.2, section 4.4 and section 5.1):
- Upper respiratory tract infections - such as sinusitis, recurrent otitis media, tonsillitis
- Lower respiratory tract infections - such as bronchitis and bronchopneumonia
- Skin and soft tissue infections - such as cellulitis, bite wounds, pyomyositis
- Skin and soft tissue infections - such as cellulitis, bite wounds, pyomyositis
- Bone and joint infections - such as osteomyelitis

ACTIMENTIN 1000 formulations will also be effective in the treatment of infections caused by amoxicillin-clavulanate organisms of the appropriate susceptibility dosage since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

4.2 Posology and method of administration
Posology
Due to the pharmacokinetic characteristics of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to prevent the development of crystalluria (see section 4.4).

General Information: For infections caused by amoxicillin-sensitive organisms the dosage is that recommended for the clavulanic acid content of the formulation (see section 5.1 for pharmacokinetic data).

Adults:
For severe infections, one ACTIMENTIN 1000 tablet every 12 hours at the start of a meal.

Special populations
Impaired renal function
Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increases with progressive renal impairment. The dose should be reduced in patients with renal impairment to delay absorption and because of the maximum recommended dose of clavulanic acid.
ACTIMENTIN 1000 should not be used in patients with a glomerular filtration rate of less than 30 ml/ minute.
Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Dose:
No dose adjustment is considered necessary.

Hepatic impairment:
Dose with caution and monitor hepatic function at regular intervals (see section 4.3 and section 4.4).

Method of administration
ACTIMENTIN 1000 is for oral use.
Tablets should be taken immediately before a meal.

Dosage Guide:
Amoxicillin-Sensitive Organisms

Upper respiratory tract infections	Lower respiratory tract infections	Urinary tract infections	Skin and soft tissue infections

Adults:

1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

Amoxicillin-Resistant Organisms:

Upper respiratory tract infections	Lower respiratory tract infections	Urinary tract infections	Skin and soft tissue infections
Haemophilus influenzae *H. influenzae* *H. parainfluenzae*	*Haemophilus influenzae* *H. parainfluenzae* *Klebsiella pneumoniae*	*Klebsiella pneumoniae*	*Staphylococcus aureus*

Adults:

1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

4.3 Contraindications
ACTIMENTIN 1000 is contraindicated in:
- Hypersensitivity to the active substances amoxicillin or clavulanic acid or to any of the excipients (see section 6.1).
- Hypersensitivity to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins has been demonstrated.
- ACTIMENTIN 1000 should not be administered to patients with a history of cholestatic jaundice/hepatic dysfunction associated with clavulanic acid.

In the case that an infection is proven to be due to an amoxicillin-susceptible organism(s) then combination should be given as monotherapy (see section 4.4 and section 5.1).

ACTIMENTIN 1000 is not suitable for use when there is a high risk that the preexisting pathogens have developed resistance to the penicillin and/or the amoxicillin-clavulanate combination (see section 4.4) by clavulanic acid. ACTIMENTIN 1000 should not be used to treat penicillin-resistant *S. pneumoniae*.

ACTIMENTIN 1000 should not be used in patients with infectious mononucleosis if a morbilliform rash has been associated with this condition following the use of amoxicillin.

ACTIMENTIN 1000 should not be given into accord in patients with a severe renal impairment (creatinine clearance of high doses is necessary.

Prolonged use may result in overgrowth of non-susceptible organisms. *Pseudomembranous enterocolitis* has been reported.

The possibility of superinfections with mycotic or bacterial pathogens should be kept mind during therapy. If superinfection occurs during treatment, appropriate measures should be taken and the patient should be discontinued and/or appropriate therapy instituted.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires ACTIMENTIN 1000 to be discontinued and any subsequent administration of amoxicillin is contraindicated.

Prolongation of prothrombin time has been reported rarely in patients receiving ACTIMENTIN 1000. Appropriate monitoring should be undertaken when prescribing anticoagulants concomitantly.

Antibiotic-associated colitis, (including *pseudomembranous colitis*, haemorrhagic colitis. *Clostridium difficile* associated diarrhoea) has also usually been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibiotic. Should antibiotic-associated colitis occur, ACTIMENTIN 1000 should immediately be discontinued, a medical practitioner be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Caution is needed when administering amoxicillin to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

When high doses are administered, adequate fluid intake and urinary output must be maintained.

Crystals in urine have been reported in patients receiving amoxicillin, usually in the early stages of administration of high doses is necessary.

ACTIMENTIN 1000 should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin-induced skin rashes.

Periodic assessment of renal, hepatic and peripheral blood haematopoietic functions, is advisable during prolonged therapy.

Impaired hepatic function: Changes in liver function tests have been observed in some patients receiving ACTIMENTIN 1000. Transient hepatitis and cholestatic jaundice have been reported. ACTIMENTIN 1000 should be used with caution in patients with evidence of hepatic dysfunction.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged therapy. These events are usually observed in adults but not in children. Signs and symptoms typically appear 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 concomitant medications which could have the potential for hepatic effects (see section 4.8).

Impaired renal function: In patients with severe renal impairment ACTIMENTIN 1000 dosage should be adjusted (see section 4.2). ACTIMENTIN 1000 should not be used in patients with a glomerular filtration rate of less than 30 ml/minute.

Use in lactation: Amoxicillin is excreted in the milk; there is no data on the excretion of clavulanic acid in human milk. Caution should be exercised when ACTIMENTIN 1000 is prescribed to a breast-feeding woman (see section 4.6).

The use of ACTIMENTIN 1000 may lead to the selection of resistant strains of organisms and sensitivity testing should, therefore, be carried out on samples taken from patients to demonstrate the appropriate sensitivity.

Interference with serological testing
It is recommended that when tested by the presence of glucose in urine during ACTIMENTIN 1000 therapy, non-enzymatic methods should be used.

Due to the high urinary concentrations of amoxicillin, false positive reactions may occur when with chemical tests.

The presence of clavulanic acid in ACTIMENTIN 1000 may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

4.5 Interaction with other medicinal products and other forms of interaction
Probenecid reduces the renal tubular secretion of amoxicillin. It does not affect clavulanic acid excretion. Concurrent use with ACTIMENTIN 1000 may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

ACTIMENTIN 1000 may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

The concomitant administration of allopurinol and amoxicillin substantially increases the incidence of skin rashes in patients receiving both drugs as compared to that observed with amoxicillin alone. It is not known whether the potentiation of amoxicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

Interactions are of clavulanic acid: Probenecid is not recommended for concurrent use with ACTIMENTIN 1000.

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature, there are reports of increased anticoagulant effects when penicillin is administered in association of warfarin and prescribed a course of amoxicillin. If coadministration is necessary, the prothrombin time should be carefully monitored when the oral anticoagulant dose is modified or before or without anticoagulant when the treatment with amoxicillin is short and anticoagulants may be necessary.

The presence of clavulanic acid in ACTIMENTIN 1000 may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

4.6 Fertility, pregnancy and lactation
Pregnancy
The safety of ACTIMENTIN 1000 during pregnancy has not been established (see section 4.3, section 4.4 and section 4.8).
No fertility data is available.

Breastfeeding
Amoxicillin is distributed into breast milk. Although significant problems in humans have not been reported, the potential of amoxicillin to cause hypersensitivity in susceptible individuals, antibiotic diarrhoea and skin rash in the infant.

Fertility
The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering at the beginning of a meal. In addition, as these symptoms are especially related to the clavulanic acid component, the dose should be adjusted to the lowest dose which will maintain an effective therapeutic level. Consideration should be given to maintaining adequate fluid intake and urinary output.

4.7 Effects on ability to drive and use machines
ACTIMENTIN 1000 has no or negligible influence on the ability to drive and use machines. However, patients should be aware of the adverse reactions (dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects
Summary of the safety profile
The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, enterocolitis, candidiasis, antibiotic colitis, urticaria, skin rash, erythema, taste, headache, dizziness, tiredness and convulsions.

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering at the beginning of a meal. In addition, as these symptoms are especially related to the clavulanic acid component, the dose should be adjusted to the lowest dose which will maintain an effective therapeutic level. Consideration should be given to maintaining adequate fluid intake and urinary output.

Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and Infestations	Frequent	Mucocutaneous candidiasis
	Less frequent	Overgrowth of non-susceptible organisms Clostridium difficile infection
Blood and the lymphatic system disorders	Less frequent	Haemolytic anaemia, reversible bromboctopenia, leucopenia, including neutropenia, reversible leukopenia and agranulocytosis, prolongation of bleeding time and prothrombin time
	Frequency unknown	Hypersensitivity reactions (Skin rashes, pruritus and urticaria, serum sickness-like reactions, angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and less frequently bullous, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) and acute epidermal necrolysis have been reported)
Immune system disorders	Frequency unknown	Hypersensitivity interstitial nephritis, Henoch-Schönlein oedema, acrid sickness-like syndrome, hypersensitivity vasculitis
Nervous system disorders	Frequent	Dyspepsia, tiredness, fever, chills
	Less frequent	Hyperactivity, convulsions, dizziness, headaches, CNS toxicity
Hepato-biliary disorders	Frequency unknown	Aseptic meningitis
	Less frequent	Diarrhoea, nausea, vomiting, indigestion, abdominal pain
Gastrointestinal disorders	Less frequent	Gastritis, stomatitis, glossitis, enterocolitis, microscopic colitis, candidiasis, antibiotic colitis (including pseudomembranous colitis and haemorrhagic colitis)
	Frequency unknown	Pigmented tooth discolouration, black hairy tongue
	Less frequent	Rises in AST/ ALT
Hepato-biliary disorders	Less frequent	Hepatitis and cholestatic jaundice
Skin and subcutaneous tissue disorders	Less frequent	Skin rashes, pruritis, urticaria and erythema multiforme
	Frequency unknown	Purpura, diaphoresis, flushing, dizziness, Stevens-Johnson syndrome, Toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders	Less frequent	Crystalluria
	Frequency unknown	Nephropathy and interstitial nephritis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to Medsafe via the "Side Effect Free Reporting Form" which can be found online under SAEFR instructions
https://www.safepug.org.nz/Publications/Index/8

4.9 Overdose
Symptoms: Overdosage with amoxicillin is usually asymptomatic. However, gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident, and symptoms of water and electrolyte imbalance may be present. Amoxicillin can precipitate in catheters, particularly in patients with renal failure. Crystalluria has been observed.

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Treatment: Adequate fluid intake and urinary output must be maintained to minimize the possibility of crystalluria.

Amoxicillin may be removed from the circulation by haemodialysis. The molecular weight, degree of protein binding and volume of distribution of clavulanic acid are such that it is considered unlikely that it will be removed with renal insufficiency. Advice on the management may also be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC code: J01CR02
Amoxicillin is a penicillin and tablets contain 7 parts (875 mg) of a broad-spectrum penicillin, amoxicillin and 1 part (125 mg) potassium clavulanate.

(i) Mechanism of Action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more penicillin-binding proteins in the biosynthetic pathway of bacterial peptidoglycan, leading to weakening of the cell wall, usually paralysis and death of the cell. The beta-lactamase enzymes produced by bacteria which are not susceptible to amoxicillin alone are inactivated by clavulanic acid. Clavulanic acid is a beta-lactam structurally related to penicillin. It inactivates many beta-lactamase enzymes commonly encountering inactivation of amoxicillin.

Potassium clavulanate has been shown *in vitro* to be an irreversible inhibitor of beta-lactamases.

The combination of amoxicillin and clavulanic acid is usually bactericidal. Tablets (Tube Type 1 Cephalosporinase) β-lactamase produced by *Acinetobacter* species, *Citrobacter* species, *Enterobacter*, *Indole positive Proteus* species, *Morganella morganii*, *Providencia rettgeri*, *Serratia* species, *Pseudomonas aeruginosa* and *penicillin-resistant staphylococci*. The presence of a β-lactamase and the activity was not reduced in the presence of serum. (*In vitro* activity does not necessarily imply *in vivo* efficacy).

(ii) Antibacterial activity
The amoxicillin component of the formulations is bactericidal for both Gram-positive and Gram-negative micro-organisms. The clavulanic acid component of the formulations is a β-lactamase inhibitor, thus, by inactivation of susceptible β-lactamases, protect amoxicillin from degradation by a large number of β-lactamase enzymes produced by penicillin-resistant strains of organisms.

(iii) Resistance
The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. The spectrum of this combination should be sought when clinical evidence of resistance is suspected. It is such that the utility of the agent in at least some types of infections is questionable.

MRSA (Staphylococcus aureus resistant to methicillin)
Inherently resistant organisms:
Acinetobacter calcoaceticus-baumannii complex
Acinetobacter sp. Citrobacter freundii Enterobacter sp.
Legionella pneumophila Morganella morganii Providencia spp.
Pseudomonas spp.
Serratia spp.
Stenotrophomonas maltophilia
Yersinia enterocolitica
Chlamydophila pneumoniae
Chlamydophila psittaci
Chlamydophila trachomatis
Mycoplasma pneumoniae

5.2 Pharmacokinetic properties
Absorption
Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The pharmacokinetic profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour. The extent to which amoxicillin and clavulanic acid are absorbed is not significantly influenced by food, although the rate of absorption is reduced, as is administration of potassium has little effect on the excretion of the clavulanic acid component of the formulation.

Distribution
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The half-life of each component is therefore prolonged in patients with renal failure, as is the risk of a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Impaired hepatic function patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data
No preclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction. Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core: Lactose monohydrate, Copovidone (Eudragit E 12.5)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)
Talc (E553b)
Magnesium stearate (E470b)
Film coat: Hypromellose (E464)
Silica colloidal anhydrous (E551)
Talc (E553b)
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30°C in a dry place. Protect from light and moisture.
Keep the blisters in the carton until required for use.

6.5 Nature and contents of container
Blister Sound foil containing of OPA/PVC sealed with aluminium lidding foil. Each blister strip contains 7 tablets. Pack size of 10 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of product
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
TRINITY PHARMA (PTY) LTD
100 16th Road,
Midrand,
1685
South Africa

8. REGISTRATION NUMBER(S)
52/20.1.0/0778

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
First authorisation: 8 February 2021

10. DATE OF REVISION OF TEXT
N.A.

SKEDULERINGSTATUS: S4

1. NAAM VAN DIE GENEESMIDDEL
ACTIMENTIN 1000 (Amoksisilien/Klavulaansuur 875 mg/125 mg, Filmbedekte tablette)

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke filmbedekte tablette bevat amoksisilientrihidraat gelyk aan 875 mg amoksisilien en kaliumklavulanaat gelyk aan 125 mg klavulaansuur.
Bevat effektiewe 2,4 mg natrium per tablet.

3. FARMASEUTIESE VORM
Filmbedekte tablette.
Wit tot effens af 22 mm by 10 mm langwerpige filmbedekte tablette met insaaglyn.
Die insaaglyn is nie bedoel vir breking vir vergemaklike van die gemak van sluk en nie te gelyke dosisse te verdeel nie.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
ACTIMENTIN 1000 is aangedui by volwassenes vir die behandeling van die volgende infeksies wat deur amoksisilien-weerstandige organismes veroorsaak word wat β-laktamases produseer wat sensitief is vir klavulaansuur (sien afdeling 4.2, afdeling 4.4 en afdeling 5.1):
- Boonste respiratoriese infeksies - soos sinusitis, herhalende otitis media, mangelontsteking
- Laer lugwegsinfeksies - soos brongitis en longinfeksies
- Vel- en sagteweefselinfeksies - soos sellulitis, bytwonde, pyomiositis
- Been- en gewrigsinfeksies - soos osteomielitis

ACTIMENTIN 1000 formulerings sal ook doeltreffend wees by die behandeling van infeksies veroorsaak deur amoksisilien-klavulaansuur-weerstandige organismes van die gepaste vatbaarheidsdosis, omdat klavulaansuur in hierdie situasie nie tot die terapeutiese uitwerking bydra nie.

4.2 Dosering en wyse van toediening
Posologie
Weens die farmakokinetiese eienskappe is dit raadsaam om voldoende vloeistofinname en urinêre uitskeiding te handhaaf om die ontwikkeling van kristalurie te voorkom (sien afdeling 4.4).

Algemene Inligting: Vir infeksies wat deur amoksisilien-sensitiewe organismes veroorsaak is, is die dosis dié soos vir amoksisilien-weerstandige, aangesien die komponent van klavulaansuur nie bydra tot die terapeutiese effek nie.

Volwassenes:
Vir ernstige infeksies, een ACTIMENTIN 1000 tablet elke 12 uur voor 'n maaltyd.

Spesiale populasies
Ingekorte nierfunksie:
Beide amoksisilien en klavulaansuur word uitgeskei deur die niere en die serumhalfleeftyd van elk neem toe by pasiente met verminderde nierfunksie. Die dosis moet verlaag word om die dosis te verminder of die interval te verleng. Dosisaanpassings is gebaseer op die maksimum aanbevole dosis van klavulaansuur.
ACTIMENTIN 1000 moet nie gebruik word by pasiente met 'n glomerulêre filtrasietempo van minder as 30 ml/minuut nie.
Hemodialise verminder serumkonsentrasies van beide amoksisilien en klavulaansuur en 'n bykomende dosis moet aan die einde van dialise toegedien word.

Bejaardes:
Geen dosisverandering word as noodsaaklik beskou.

Hepatiese inkorting:
Gebruik met omgewing en monitor die lewerfunksie met gereelde tussenposes (sien afdeling 4.3 en 4.4).

Metode van toediening
ACTIMENTIN 1000 is vir orale gebruik.
Tablette moet onmiddellik voor die gebeure word.

Dosisriglyn:
Amoksisilien-Sensitiewe Organismes:

Boonste lugweg-infeksies	Onderste lugweg-infeksies	Urienwegtoksiese	Vel- en sagteweefselinfeksies
1 tablet 12-uurliks	1 tablet 12-uurliks	1 tablet 12-uurliks	1 tablet 12-uurliks

Volwassenes:

1 tablet 12-uurliks	1 tablet 12-uurliks	1 tablet 12-uurliks	1 tablet 12-uurliks

Amoksisilien-Weerstandige Organismes:

Boonste lugweg-infeksies	Onderste lugweg-infeksies	Urienwegtoksiese	Vel- en sagteweefselinfeksies
Haemophilus influenzae *H. influenzae* *H. parainfluenzae*	*Haemophilus influenzae* *H. parainfluenzae* *Klebsiella pneumoniae*	*Klebsiella pneumoniae*	*Staphylococcus aureus*

Volwassenes:

1 tablet 12-uurliks	1 tablet 12-uurliks	1 tablet 12-uurliks	1 tablet 12-uurliks

4.3 Kontraindikasies
ACTIMENTIN 1000 is kontraindikeer in:
- Hipersensitiwiteit vir die aktiewe substansies amoksisilien of clavulanic acid or to any of the excipients (see section 6.1).
- Hipersensitiwiteit to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins has been demonstrated.
- ACTIMENTIN 1000 should not be administered to patients with a history of cholestatic jaundice/hepatic dysfunction associated with clavulanic acid.

In die case that an infection is proven to be due to an amoksisilien-susceptible organism(s) then combination should be given as monotherapy (see section 4.4 and section 5.1).

ACTIMENTIN 1000 is nie suitable for use when there is a high risk that the preexisting pathogens have developed resistance to the penicillin and/or the amoksisilien-clavulanate combination (see section 4.4) by clavulanic acid. ACTIMENTIN 1000 should not be used to treat penicillin-resistant *S. pneumoniae*.

ACTIMENTIN 1000 should not be used in patients with infectious mononucleosis if a morbilliform rash has been associated with this condition following the use of amoksisilien.

ACTIMENTIN 1000 should not be given into accord in patients with a severe renal impairment (creatinine clearance of high doses is necessary.

Prolonged use may result in overgrowth of non-susceptible organisms. *Pseudomembranous enterocolitis* has been reported.

The possibility of superinfections with mycotic or bacterial pathogens should be kept mind during therapy. If superinfection occurs during treatment, appropriate measures should be taken and the patient should be discontinued and/or appropriate therapy instituted.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires ACTIMENTIN 1000 to be discontinued and any subsequent administration of amoksisilien is contraindicated.

Prolongation of prothrombin time has been reported rarely in patients receiving ACTIMENTIN 1000. Appropriate monitoring should be undertaken when prescribing anticoagulants concomitantly.

Antibiotic-associated colitis, (including *pseudomembranous colitis*, haemorrhagic colitis. *Clostridium difficile* associated diarrhoea) has also usually been reported with nearly all antibacterial agents including amoksisilien and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibiotic. Should antibiotic-associated colitis occur, ACTIMENTIN 1000 should immediately be discontinued, a medical practitioner be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Caution is needed when administering amoksisilien to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

When high doses are administered, adequate fluid intake and urinary output must be maintained.

Crystals in urine have been reported in patients receiving amoksisilien, usually in the early stages of administration of high doses is necessary.

ACTIMENTIN 1000 should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoksisilien-induced skin rashes.

Periodic assessment of renal, hepatic and peripheral blood haematopoietic functions, is advisable during prolonged therapy.

Impaired hepatic function: Changes in liver function tests have been observed in some patients receiving ACTIMENTIN 1000. Transient hepatitis and cholestatic jaundice have been reported. ACTIMENTIN 1000 should be used with caution in patients with evidence of hepatic dysfunction.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged therapy. These events are usually observed in adults but not in children. Signs and symptoms typically appear 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 concomitant medications which could have the potential for hepatic effects (see section 4.8).

Impaired renal function: In patients with severe renal impairment ACTIMENTIN 1000 dosage should be adjusted (see section 4.2). ACTIMENTIN 1000 should not be used in patients with a glomerular filtration rate of less than 30 ml/minute.

Use in lactation: Amoksisilien is excreted in the milk; there is no data on the excretion of clavulanic acid in human milk. Caution should be exercised when ACTIMENTIN 1000 is prescribed to a breast-feeding woman (see section 4.6).

Die gebruik van ACTIMENTIN 1000 may lead to die selection of resistant strains of organisms and sensitivity testing should, therefore, be carried out on samples taken from patients to demonstrate the appropriate sensitivity.

Interference with serological testing
It is recommended that when tested by the presence of glucose in urine during ACTIMENTIN 1000 therapy, non-enzymatic methods should be used.

Due to the high urinary concentrations of amoksisilien, false positive reactions may occur when with chemical tests.

The presence of clavulanic acid in ACTIMENTIN 1000 may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

4.5 Interaksie met ander geneesmiddelprodukte en ander vorme van interaksie
Probenesied verlaag die renale tubulêre sekresie van amoksisilien, maar affekteer nie klavulaansuuruitskeiding nie. Gelyktydige gebruik met ACTIMENTIN 1000 kan lei tot verhoogde en verlengde bloedvlakke van amoksisilien maar nie van klavulaansuur nie.

ACTIMENTIN 1000 kan die doeltreffendheid van mondelinge voorbehoedmiddels verminder en patiënte moet dienooreenkomstig gewaarsku word.

Die gelyktydige toediening van allopurinol en amoksisilien verhoog die voorkoms van velreaksies in pasiënte wat albei middels ontvang in vergelyking met dié wat amoksisilien alleen ontvang. Dit is nie bekend of hierdie verergering van amoksisilienuitslag plaasvind weens allopurinol of die hiperurisemie teenwoordig in hierdie pasiënte nie.

Interaksies in ander bakteriële antibiotika geneesmiddels mag inmeng met die bakteriesidale uitwerking van amoksisilien.

Mondelinge antikoagulante en penisillienantibiotika word in die praktyk wyd gebruik sonder gerapporteerde interaksie. Nietemin, in die literatuur, is daar verslae van verhoogde antikoagulantaktiwiteit wanneer penisillien geassosieer word met 'n kursus amoksisilien voorgeskryf. Indien gelyktydige toediening noodsaaklik is, moet die protrombientyd sorgvuldig gemonitor word wanneer die orale antikoagulantdosis gewysig word of voor of sonder antikoagulant wanneer die behandeling met amoksisilien kort is en antikoagulante dalk nodig is vir die bepaling.

Penisillene kan die uitskeiding van metotreksaat vermeder, wat 'n potensiële bomane in toksisiteit kan veroorsaak.

By pasiënte wat mikofenolsuurbevattende middels, is 'n vermindering van die aktiewe metaboliet mikofenolsuur (MPA) van ongeveer 50% waargeneem tussen dae voor en onmiddellik na die aanvang van mondelinge amoksisilien plus klavulaansuur. Die verandering in die voor-dosis vlak kan die verandering in die totale MPA-blootstelling nie weerspieël nie. Daarbenewens is geen veranderinge in die klinies aanvaarbare tyd tot transplantaatverwerping waargeneem by pasiënte wat amoksisilien plus klavulaansuur as deel van hul voortsetting van die anti-m.w. Nuukerige kliniese monitering moet egter tydens die kombinasie en kort daarna asook by die staking van amoksisilien gedoen word.

Daar is verslae van positiewe toetsresultate met behulp van 'n Aspergillus O/B-toets by pasiënte wat amoksisilien-klavulaansuur ontvang het. Vals-positiewe reaksies met hierdie toets by pasiënte wat amoksisilien-klavulaansuur ontvang het, word gerapporteer. Daarom moet die positiewe toets van Aspergillus as gevolg van pasiënte wat amoksisilien-klavulaansuur ontvang, met versigtigheid geïnterpreteer word en bevestigende laboratoriumtoetse moet gedoen word.

4.6 Vrugbaarheid, swangerskap en laktasie
Swangerskap (Kategorie B1) – Slegs toegelaat onder bepaling by mans en vroue.
Die veiligheid van ACTIMENTIN 1000 tydens swangerskap is nie vasgestel nie (sien afdeling 4.3, afdeling 4.4 en afdeling 4.8).
Geen vrugbaarheidsdata is beskikbaar nie.

Laktasie
Amoksisilien word in borsmelk versprei. Alhoewel daar nie ernstige probleme by mense gedokumenteer is nie, kan die gebruik van amoksisilien deur moeders wat borsvoed, to fot sensitiwiteite, diarree, velreaksies en candidiasis by die baba lei.

Vrugbaarheid
Geen vrugbaarheidsdata is beskikbaar nie.

4.7 Effekte op vermoë om te bestuur en masjiene te gebruik
ACTIMENTIN 1000 het geen of 'n weglaatbare invloed op die vermoë om te bestuur en masjiene te gebruik nie. Pasiënte moet egter bewus wees van die negatiewe reaksies (duiseligheid, konvulsies), wat die vermoë om te bestuur en masjiene te gebruik kan beïnvloed (sien afdeling 4.8).

4.8 Ongewenste effekte
Opsomming van die veiligheidsprofiel
Die algemeenste gerapporteerde newe-effekte (ADR's) is diarree, naarheid, braking, sleg spysvertering, stomatitis, glossitis, enterokolitis, candidiasis, antibiotiese kolitis, urtikaria, veluitslag, geelsug, duiseligheid, hoofpyn, moegheid en konvulsies.

Die voorkoms en erns van newige uiteenlopings, veral naarheid en diarree, het toegeneem met die hoër aanbevole dosis en kan tot die minimum beperk word deur dit met die begin van 'n maaltyd toe te dien. Daarbenewens, aangesien hierdie simptome veral verband hou met die kaliumklavulaansuur komponent, moet die dosis aangepas word tot die laagste dosis wat 'n doeltreffende terapeutiese vlak sal handhaaf. Oorweging moet gegee word om die voldoende vloeistofinname en urinêre uitskeiding te handhaaf.

Tabulasie van bywerkings

Sistemiese Organklas	Frekwensie	Newige reaksies
Infeksies en Infestasies	Gereeld	Hipersensitiwiteit, allergiese reaksies (pruritis, urtikaria, eksantem, uitslag, angioneurotiese oedeem, tagkardie, hipotensie en hipertensie), anafilaktiese skok, serum-siekte-agtige reaksies, angioneurotiese oedeem, bloedvloei
	Minder gereeld	Hoofpyn
	Frekwensie onbekend	Sinkope, stuiptrekkings
Oogaflewings	Minder gereeld	Duisee sig
Oor- en labirintaflewings	Minder gereeld	Tinnitus
Hartaflewings	Minder gereeld	Hartaanval
Vaskulêre afwykings	Minder gereeld	Bloedings
	Frekwensie onbekend	Glosite, sweet
Asemhalings-, borskas en mediastinumafwykings	Minder gereeld	Rinoree, bronkospasme, dispnee
Gastro-intestinale afwykings	Minder gereeld	Hemoptise, asemhalingsaanval
	Minder gereeld	Braking, naarheid, stomatitis, glossitis, diarree, dispepsie, sooibloed
Hepato-bilière afwykings	Frekwensie onbekend	Verstoringe in lewerfunksie
Nier- en suilsiekteafwykings	Frekwensie onbekend	Uriklare
Voortplantingstelsel- en borsafwykings	Frekwensie onbekend	Edeem van die geslag
Spier- en bindweefselafwykings	Frekwensie onbekend	Artralgie
Algemene afwykings en toedieningsplekkitsdoeninge	Minder gereeld	Pyreksie, koukouers
Ondersoeke	Minder gereeld	Lae bloedtruk
	Frekwensie onbekend	Aanlose

(i) Staak-en-vermoë om te behoue en magiese te gebruik
ACTIMENTIN 1000 het geen of 'n weglaatbare invloed op die vermoë om te bestuur en masjiene te gebruik nie. Pasiënte moet egter bewus wees van die negatiewe reaksies (duiseligheid, konvulsies), wat die vermoë om te bestuur en masjiene te gebruik kan beïnvloed (sien afdeling 4.8).

(ii) Opgenoming van bywerkingsreaksies
Die opgenoming van bywerkingsreaksies na magtiging van die middel is belangrik. Dit laat voortgesette monitering van die voordeel/risiko-balans van die middel toe. Gesondheidsorgverskaffers word gevra om enige vermoedelike bywerkingsreaksies aan Medsafe te rapporteer via die "Side Effect Free Reporting Form", wat aanlyn gevind word onder SAFRA se publikasies
https://www.safepug.org.nz/Publications/Index/8

4.9 Oordosering
Simptome: Oordosering met amoksisilien is gewoonlik asimptomaties. Gastrointestinale effekte soos naarheid, braking en diarree kan egter voorkom, asook simptome van water- en elektrolietonbalans. Amoksisilien kristalliseer maklik in kateters, veral in pasiënte met nierversaking. Kristalluria is waargeneem.

Konv