1. NAME OF THE MEDICINAL PRODUCT

1.1 (Invented) Name of the Medicinal Product

TUNACLAV 457 DT

Dispersible Co-Amoxiclav Tablets BP 457 mg

1.2 Strength

Amoxicillin 400 mg
Clavulanic Acid 57 mg

1.3 Pharmaceutical Form

Oral, Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uncoated Despersible tablets contains:
Amoxicillin Trihydrate BP
Eq. to Amoxicillin 400mg
Diluted Potassium Clavulanate BP
Eq. to Clavulanic Acid 57 mg
Excipients q.s

Sr. No.	Ingredient	Specification	Overages	Quantity in mg per tablet
1	Amoxicillin Trihydrate	BP	2.0 %	468.302
2	Diluted Potassium Clavulanate	BP	3.0 %	139.847
3	Crospovidone	BP	--	Q.s.
4	Colloidal Silicon Dioxide	BP	--	Q.s.
5	Microcrystalline Cellulose PH-112	BP	--	Q.s.
6	Silicon Dioxide	BP	--	Q.s.
7	Magnesium Sterate	BP	--	Q.s.
8	Croscarmellose Sodium	BP	--	Q.s.
9	Microcrystalline cellulose Plain	BP	--	Q.s.
10	Doshion-544 D	BP	--	Q.s.
11	Purified Talc	BP	--	Q.s.

12	Trusil Strawberry Flavour	IH	--	Q.s.
13	Trusil Peppermint Flavour	IH	--	Q.s.
14	Aspartame	BP	--	Q.s.
Total weight				1000.00 mg

* The quantity of Amoxycillin Trihydrate to be taken on 100% assay basis inclusive of 2.0% overages. Actual quantity to be used after calculation of assay of Amoxycillin Trihydrate on as such basis.

*The quantity of Potassium Clavulanate Diluted to be taken on 100% assay basis inclusive of 3.0% overages. Actual quantity to be used after calculation of assay of Potassium Clavulanate on as such basis.

3. PHARMACEUTICAL FORM

Oral solid dosage form, Dispersible Tablets

Off white to light yellow coloured Speckled, elongated shape, biconvex, both side plain uncoated dispersible tablets. Free from any obvious defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin/Clavulanic Acid tablets is indicated for the treatment of the following infections in adults and children:
Acute bacterial sinusitis (adequately diagnosed)
Cystitis
Pyelonephritis
Cellulitis
Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
Bone and joint infections, in particular osteomyelitis.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of amoxicillin/clavulanic acid that is selected to treat an individual infection should take into account:
• The expected pathogens and their likely susceptibility to antibacterial agents
• The severity and the site of the infection
• The age, weight and renal function of the patient as shown below.
The use of alternative presentations of amoxicillin/clavulanic acid (e.g. those that provide higherdoses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should beconsidered as necessary.
For adults and children≥40 kg, <Amoxicillin/Clavulanic acid> 500/125 tablets provide a totaldaily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommendedbelow. For children < 40 kg, <Amoxicillin/Clavulanic acid> 125/31.25 and 250 mg/62.5 mgtablets provide a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, whenadministered as recommended below. If it is considered that a higher daily dose of amoxicillin isrequired, it is recommended that another preparation of amoxicillin/clavulanic acid is selected inorder to avoid administration of unnecessarily high daily doses of clavulanic acid.

Adults and children≥40 kg
One 500/125 mg dose taken three times a day.
Children < 40 kg
20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.
Children may be treated with (dispersible) tablets, suspensions or paediatric sachets. Childrenaged 6 years and below should preferable be treated with Amoxicillin/Clavulanate dispersible Tablets (dispersed), suspension or paediatric sachets.
No clinical data are available on doses of amoxicillin/clavulanic acid 4:1 formulations higher than40 mg/10 mg/kg per day in children under 2 years.

Method of administration
Amoxicillin/clavulanic acid tablets are for oral use.
Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.
Therapy can be started parenterally according to the SPC of the IV-formulation and continued with an oral preparation.
Amoxicillin/clavulanic acid tablets can be swallowed whole with a glass of water, or should bestirred into a little water before taking.
For children with weight < 40 kg it is recommended to stir the tablets into a little water before taking.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in.
History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another betalactam agent (e.g. a cephalosporin, carbapenem or monobactam). History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made on cerning previous hypersensitivity reactions to penicillins, cephalosporins or other betalactam agents.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Amoxicillin/clavulanic acid is not suitable for use when there is a high risk that the presumptivepathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by betalactamases susceptible to inhibition by clavulanic acid (e.g. penicillin-insusceptible *S. pneumoniae*).

Convulsions may occur in patients with impaired renal function or in those receiving high doses Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since theoccurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.Prolonged use may occasionally result in overgrowth of nonsusceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustule may be a symptom of acute generalised exanthemous pustulosis (AGEP).

This reaction requires Amoxicillin/clavulanic discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment .Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, 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.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening .Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function isadvisable during prolonged therapy.Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

In patients with renal impairment, the dose should be adjusted according to the degree of impairment. In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria.

In patients with bladder catheters, a regular check of patency should be maintained. During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with nonenzymatic methods.

The presence of clavulanic acid in Amoxicillin/Clavulanic acid may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test. in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

4.6 Pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Lactation:
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.
The ADRs derived from clinical studies and post-marketing surveillance with Amoxicillin/clavulanic, sorted by MedDRA System Organ Class are listed below.
The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare

Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Aeseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known

Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.

[4] Including pseudomembranous colitis and haemorrhagic colitis .

[5] A moderate rise in AST and/or ALT has been noted in patients treated with betalactam class antibiotics, but the significance of these findings is unknown. [6] These events have been noted with other penicillins and cephalosporins If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained.

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors

ATC code: J01CR02.

Mode of action:

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.
Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.
Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some betalactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

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 plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers, are presented below.

Mean (± SD) pharmacokinetic parameters

Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC (0-24h) ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 0.12

AMX – amoxicillin, CA – clavulanic acid *
Median (range)

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk. Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces, and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Amoxicillin/clavulanic 250 mg/125

mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.
Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.
Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
Gender
Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid. Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as 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.
Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.
Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.
Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its component.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Silicon Dioxide
Colloidal Silicon Dioxide
Magnesium Stearate
Croscarmellose sodium
Microcrystalline cellulose Plain
Microcrystalline cellulose pH-112
Purified talc
Doshion-544 D
Trusil Strawberry flavour

Trusil peppermint Flavour
Aspartame

6.2 Incompatibilities

None

6.3 Shelf life 24

months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place, protected from light.

6.5 Nature and contents of container

Aluminium Strip pack of 1x10 tablets packed in a carton along with package insert.

6.6 Special precautions for disposal

No special requirements

7.REGISTRANT MARKETING AUTHORISATION HOLDER Radiance Pharmaceuticals Limited,
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8. DATE OF REVISION OF THE TEXT

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