

<b>Summary of Product Characteristics</b>
---

**1-NAME OF THE MEDICINAL PRODUCT (FPP)**

Dafraclav® 1000 mg BD

*Amoxicilin - Clavulanic Acid*

**1.1. Strength**

875 mg + 125 mg

**1.2. Pharmaceutical form**

Filmcoated tablet

**2- QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid.

For the full list of excipients, see section 6.1.

**3- PHARMACEUTICAL FORM**

Film-coated tablet.

White to off-white, oblong , one side scored , one side engraved "KF".

**4- CLINICAL PARTICULARS****4.1 Therapeutic indications**

Dafraclav 1000 mg BD is indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis
- Acute otitis media
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Cystitis
- Pyelonephritis

- 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 mode of administration**

### **4.2.1 Posology**

#### **Adults and children $\geq 12$ years**

One tablet of Dafraclav 1000 mg BD twice a day.

### **4.2.2 Special populations**

#### **Elderly**

No dose adjustment is deemed necessary.

#### **Hepatic insufficiency**

Use with caution and monitor liver function at regular intervals.

#### **Renal failure**

- No dose adjustment is necessary in patients with creatinine clearance (CrCl) greater than 30 ml / min.
- Adults and children with body weight of 40 kg or more( Dafraclav is also available in tablets of 500mg/125mg):
  - In patients with a creatinine clearance 10-30 ml / min: 500 mg/125 mg twice daily
  - In patients with a creatinine clearance < 10 ml / min: 500 mg/125 mg once daily
  - Haemodialysis: 500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

---

### 4.2.3 Pediatric population

Since the Dafraclav 1000 mg BD film coated tablet cannot be divided, other forms of Dafraclav are available for children.

- For children under 12 years of age and with a body weight of more than 40 kg, Dafraclav is available in suspension containing 400 mg of amoxicillin and 57 mg of clavulanic acid per 5 ml of reconstituted suspension or as tablet of 500 mg of amoxicillin and 125 mg of clavulanic acid.
- For children below 40 kg body weight, Dafraclav is available in suspension containing 400 mg of amoxicillin and 57 mg per 5 ml of reconstituted suspension or in suspension containing 200 mg of amoxicillin and 28 mg of clavulanic acid per 5 ml of reconstituted suspension.

### 4.2.4 Method of administration

Dafraclav 1000 mg BD is for oral use.

To minimize potential gastrointestinal intolerance, Dafraclav 1000 mg Tablets should be administered at the start of a meal.

### 4.3 Contraindications

- Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another  $\beta$ -lactam agent (e.g. a cephalosporin, carbapenem or monobactam).
- History of jaundice or hepatic impairment due to amoxicillin/clavulanic acid.

### 4.4 Special warning and precautions for use

#### 4.4.1 General information

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other  $\beta$ -lactam 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 organism(s) then switching from amoxicillin/clavulanic acid to amoxicillin should be considered in accordance with official guidance.

The use of Dafraclav 1000 mg BD is not suitable when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to  $\beta$ -lactam agents that is not mediated by  $\beta$ -lactamases susceptible to inhibition by clavulanic acid. Amoxicillin/clavulanic acid should not be used to treat penicillin-resistant *S. pneumoniae*.

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

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence 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 non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP). This reaction requires discontinuation of the treatment with Dafraclav 1000 mg Tablets and contraindicates any subsequent administration of amoxicillin.

In patients with evidence of hepatic impairment amoxicillin/clavulanic acid should be used with caution. 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 including amoxicillin and may range in severity from mild to life threatening. Therefore,

it is important to consider this diagnosis in patients who present with diarrhea 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 contraindicated in this situation.

During prolonged therapy periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable.

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.

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 non-enzymatic methods.

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

There have been reports of positive test results using the Bio-Rad Laboratories Platelia Aspergillus EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods

---

#### 4.4.2 Pediatric population

Dafraclav 1000 mg BD is an adult form of amoxicillin/clavulanic acid and should not be used in children weighing less than 40 kg.

#### 4.5 Interactions with other medicinal products and other forms of interactions

##### 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 normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

##### Methotrexate

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

##### Probenecid

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

##### Mycophenolate mofetil

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

## **4.6 Pregnancy, lactation and fertility,**

### **4.6.1 Pregnancy**

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). 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 fetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotizing enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

### **4.6.2 Lactation**

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhea 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 sensitization should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician.

### **4.6.3 Fertility**

There are no data on the effects of amoxicillin or clavulanic acid on human fertility. Animal reproduction studies have shown no effect on fertility.

## **4.7 Effects on the ability to drive and use machines**

Effects on the ability to drive and use machines have not been studied. 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 diarrhea, nausea and vomiting.

The following terminologies have been used in order to classify the occurrence of undesirable effects: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  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).

System organ Class/ Undesirable effect	Frequency
<b><i>Infections and infestations</i></b>	
Mucocutaneous candidosis	common
Overgrowth of non-susceptible organisms	not known
<b><i>Blood and lymphatic system disorders</i></b>	
Reversible leucopenia (including neutropenia)	rare
Thrombocytopenia	rare
Reversible agranulocytosis	not known
Hemolytic anemia	not known
Prolongation of bleeding time and prothrombin time	not known
<b><i>Immune system disorders<sup>1</sup></i></b>	
Angioneurotic edema	not known
Anaphylaxis	not known
Serum sickness-like syndrome	not known
Hypersensitivity vasculitis	not known
<b><i>Nervous system disorders</i></b>	
Dizziness	uncommon
Headache	uncommon
Reversible hyperactivity	not known
Convulsions	not known
Aseptic meningitis	not known
<b><i>Gastrointestinal disorders</i></b>	
Diarrhea	very common
Nausea	common
Vomiting	common
Indigestion	uncommon
Antibiotic-associated colitis	not known
Black hairy tongue	not known
<b><i>Hepatobiliary disorders</i></b>	
Rises in AST and/or ALT	uncommon
Hepatitis	not known
Cholestatic jaundice	not known
<b><i>Skin and subcutaneous tissue disorders<sup>7</sup></i></b>	
Skin rash	uncommon



System organ Class/ Undesirable effect	Frequency
Pruritus	uncommon
Urticaria	uncommon
Erythema multiforme	rare
Stevens-Johnson syndrome	not known
Toxic epidermal necrolysis	not known
Bullous exfoliative-dermatitis	not known
Acute generalized exanthemous pustulosis (AGEP)	not known
<b><i>Renal and urinary disorders</i></b>	
Interstitial nephritis	not known
Crystalluria	not known

## 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 hemodialysis.

## 5- PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinatins of penicillins, including  $\beta$ -lactamase inhibitors

ATC code: J01CR02

### Mechanism 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, 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  $\beta$ -lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

### Pharmacodynamic - Pharmacokinetic relationship

The time above the minimum inhibitory concentration ( $T > MIC$ ) is considered to be the major determinant of efficacy for amoxicillin.

### Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial  $\beta$ -lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

### Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

organism	susceptibility breakpoints ( $\mu\text{g/ml}$ )		
	<i>susceptible</i>	<i>intermediate</i>	<i>resistant</i>
<i>Haemophilus influenzae</i> <sup>1</sup>	$\leq 1$	-	$> 1$
<i>Moraxella catarrhalis</i> <sup>1</sup>	$\leq 1$	-	$> 1$
<i>Staphylococcus aureus</i> <sup>2</sup>	$\leq 2$	-	$> 2$
Coagulase-negative staphylococci <sup>2</sup>	$\leq 0.25$		$> 0.25$
<i>Enterococcus</i> <sup>1</sup>	$\leq 4$	8	$> 8$

<i>Streptococcus A, B, C, G</i> <sup>5</sup>	≤ 0.25	-	> 0.25
<i>Streptococcus pneumoniae</i> <sup>3</sup>	≤ 0.5	1-2	> 2
Enterobacteriaceae <sup>1,4</sup>	-	-	> 8
Gram-negative Anaerobes <sup>1</sup>	≤ 4	8	> 8
Gram-positive Anaerobes <sup>1</sup>	≤ 4	8	> 8
Non-species related breakpoints <sup>1</sup>	≤ 2	4-8	> 8

1. The reported values are for amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.
2. The reported values are oxacillin concentrations.
3. Breakpoint values in the table are based on ampicillin breakpoints.
4. The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
5. Breakpoint values in the table are based on benzylpenicillin breakpoints.

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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

#### Commonly susceptible species

- Aerobic Gram-positive micro-organisms
  - *Enterococcus faecalis*
  - *Gardnerella vaginalis*
  - *Staphylococcus aureus* and coagulase-negative staphylococci (methicillin-susceptible, all methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid.)
  - *Streptococcus agalactiae*
  - *Streptococcus pneumoniae* (*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid.)
  - *Streptococcus pyogenes* and other β-hemolytic streptococci
  - *Streptococcus viridans* group
- Aerobic Gram-negative micro-organisms
  - *Capnocytophaga* spp.
  - *Eikenella corrodens*
  - *Haemophilus influenzae*

- 
- *Moraxella catarrhalis*
  - *Pasteurella multocida*
  - Anaerobic micro-organisms
    - *Bacteroides fragilis*
    - *Fusobacterium nucleatum*
    - *Prevotella* spp.

#### **Species for which acquired resistance may be a problem**

- Aerobic Gram-positive micro-organisms
  - *Enterococcus faecium*
- Aerobic Gram-negative micro-organisms
  - *Escherichia coli*
  - *Klebsiella oxytoca*
  - *Klebsiella pneumoniae*
  - *Proteus mirabilis*
  - *Proteus vulgaris*

#### **Inherently resistant organisms**

- Aerobic Gram-negative micro-organisms
  - *Acinetobacter* sp.
  - *Citrobacter freundii*
  - *Enterobacter* sp.
  - *Legionella pneumophila*
  - *Morganella morganii*
  - *Providencia* spp.
  - *Pseudomonas* sp.
  - *Serratia* sp.
  - *Stenotrophomonas maltophilia*
- Other micro-organisms
  - *Chlamydophila pneumoniae*
  - *Chlamydophila psittaci*
  - *Coxiella burnetti*
  - *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 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 (875 mg/125 mg tablets two times daily) was administered in the fasting state to groups of healthy volunteers are presented below:

<b>Mean (<math>\pm</math> SD) pharmacokinetic parameters</b>					
Active substance(s) administered	Dose	$C_{max}$	$T_{max}^1$	AUC (0-	$T_{1/2}$
	(mg)	( $\mu$ g/ml)	(h)	( $\mu$ g.h/ml)	(h)
<b>Amoxicillin</b>					
Amoxicillin/clavulanic acid 875/125 mg	875	11.64 $\pm$ 2.78	1.50 (1.0-2.5)	53.52 $\pm$ 12.31	1.19 $\pm$ 0.21
<b>Clavulanic acid</b>					
Amoxicillin/clavulanic acid 875/125 mg	125	2.18 $\pm$ 0.99	1.25 (1.0- 2.0)	10.16 $\pm$ 3.04	0.96 $\pm$ 0.12

<sup>1</sup> 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 feces, and as carbon dioxide in expired air.

**Elimination**

The major route of elimination for amoxicillin is via the kidneys, 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 hours after administration of single tablets with amoxicillin/clavulanic acid 250 mg/125 mg or 500 mg/125 mg. 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.

*Pediatric population*

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.

*Geriatric population*

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and to monitor renal function may be useful.

*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.

*Patients with 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.

*Patients with hepatic impairment*

Patients with hepatic impairment 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 discolored tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.6-

**6- PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Tablet core:

- Croscarmellose sodium,
- Colloidal anhydrous silica,
- Magnesium stearate,
- Microcrystalline cellulose.

Tablet film coating:

- Opadry white OY-S-7191, contains Titanium dioxide (E171), Hypromellose, Propylene glycol and Ethylcellulose

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

Store below 30°C. Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

Cardboard box with 10 film coated tablets in aluminium/aluminium blister (2 blisters of 5 tablets).

**6.6 Special precautions for disposal and other handlings**

Any unused medicine or waste must be disposed of in accordance with the regulations in force.

**7- MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS****7.1 Marketing Authorisation Holder**

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

**7.2 Manufacturer**

Bilim Pharmaceuticals. Çerkezköy Plant, 59501 Çerkezköy/Tekirdağ, Turkey.

**8- MARKETING AUHORISATION NUMBER**

See list of MAs per country

**9- DATE OF FIRST REGISTRATION**

See list of MAs per country

**10- DATE OF REVISION OF TEXT**

June 2019