IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0111/004/001
Case No: 2064165

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Sandoz GmbH

Biochemiestrasse 10, **A-6250 Kundl**, **Austria**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Amoxicillin Sandoz 250 mg capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **22/07/2009** until **13/09/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amoxicillin Sandoz 250 mg capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg amoxicillin (as trihydrate)

For a full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Capsule, hard
Yellow, opaque capsules with black imprints alternately “AMX” and "250" axially
(if appropriate)

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amoxicillin Sandoz is indicated for the oral treatment of the following bacterial infections caused by amoxicillin-sensitive gram-positive and gram-negative pathogens (see section 5.1.):

- Infections of the upper respiratory tract, including infections of the ears, nose and throat: Acute otitis media, acute sinusitis and bacterial pharyngitis
- Infections of the lower respiratory tract: Acute exacerbation of chronic bronchitis, community-acquired pneumonia
- Infections of the lower urinary tract: Cystitis
- Endocarditis: Prophylaxis of endocarditis in patients at risk i.e. surgery in the oral cavity or upper airways.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.
Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

4.2 Posology and method of administration

Posology
The dosage of amoxicillin is dependent on age, bodyweight and renal function of the patient, on the seriousness and localisation of the infection and on the expected or proved causative agent.

Standard dosage:

Adults and adolescents (> 40 kg body weight):

The usual dosage covers a range from 750 mg to 3g amoxicillin daily in three divided doses. In some areas 1500 mg amoxicillin daily in three divided doses are recommended as the upper usual dose.

Special dosage recommendation
Acute exacerbation of chronic bronchitis in adults: 2 x 1 g per day

Children (under 12 years)
For infants and children oral suspensions containing amoxicillin are recommended.

Dosage for the prevention of endocarditis:

For the prevention of endocarditis, in patients not having general anaesthetic**,** 3 g amoxicillin are given in the hour preceding the surgical procedure, followed by (6 hours later) a further 3 g dose, if considered necessary.
For further details and description of risk patients local official guidelines for the prevention of endocarditis should be consulted

Dosage in impaired renal function:

The dose should be reduced in patients with severe renal function impairment. In patients with a renal clearance of less than 30 ml/min an increase in the dosage interval or a reduction in the subsequent doses is recommended (see section 4.4). Short course treatments with a single dose of 3 g cannot be given in case of renal failure.

Adults including elderly patients		
Creatinine clearance ml/min	Dose	Interval; between administration
> 30	No adjustment necessary	
10-30	500 mg	12 h
<10	500 mg	12h
In case of human hemodialysis 500 mg should be administered at the end of the procedure		

Dosage in impaired hepatic function
No dose reduction is necessary as long as the renal function is not impaired.

Duration of therapy:

In general the therapy should be continued for 2 to 3 days following the disappearance of symptoms. In β-haemolytic streptococcal infections the duration of therapy should be at least 10 days in order to achieve eradication of the organism.
Parenteral therapy is indicated if the oral route is considered impracticable or unsuitable, and particularly for the urgent treatment of severe infection.

Method of administration:

The preparations are administered orally.

Amoxicillin Sandoz capsules should be taken unchewed with liquid (e.g. a glass of water).

The absorption of amoxicillin is not reduced by food intake.

4.3 Contraindications

Amoxicillin Sandoz is contraindicated in patients with:

- Hypersensitivity to penicillin; a cross-allergy to other beta-lactams such as cephalosporins should be taken into account.
- Hypersensitivity to any of the other ingredients in the product

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins and cephalosporins. The possibility of cross-hypersensitivity (10 % - 15 %) with cephalosporins should be taken into account.

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 hypersensitivity to beta-lactam antibiotics.

Patients suffering from severe gastrointestinal disturbances with diarrhoea and vomiting should not be treated with Amoxicillin Sandoz, due to the risk of reduced absorption. In these cases a parenteral treatment with amoxicillin is advisable.

Amoxicillin Sandoz should be used with caution in patients with allergic diathesis and asthma.

In patients with renal function impairment the excretion of amoxicillin will be delayed and, depending on the degree of the impairment, it may be necessary to reduce the total daily dosage (see section 4.2.).

In patients with renal function impairment the excretion of amoxicillin will be delayed and, depending on the degree of the impairment, it may be necessary to reduce the total daily dosage (see section 4.2.).

The prolonged use of amoxicillin may occasionally result in an overgrowth of non-susceptible organisms or yeasts. Patients should therefore carefully be watched for superinfections.

The occurrence of anaphylactic shock and other severe allergic reactions is rare following the oral administration of amoxicillin.

However, if such reactions occur, appropriate emergency treatment measures must be taken: I.v. administration of epinephrine, followed by antihistaminic drugs, volume substitution and administration of glucocorticoids. Patients should be kept under close observation, and further therapeutic measures (artificial respiration, oxygen) should be administered as required.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.
At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria.

Amoxicillin Sandoz should be used with caution in patients with viral infections, acute lymphatic leukaemia, or infectious mononucleosis (due to an increased risk of erythematous skin rashes).

Pseudomembranous colitis should be borne in mind if severe persistent diarrhoea occurs (in most cases caused by *Clostridium difficile*). In this case Amoxicillin Sandoz should be discontinued and an adequate therapy has to be started. The use of antiperistaltics is contraindicated.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended
Allopurinol
Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions and is therefore not advised.

Digoxin
An increase in the absorption of digoxin is possible on concurrent administration with amoxicillin. A dose adjustment of digoxin may be necessary.

Disulfiram
Simultaneous administration of disulfiram is not recommended.

Anticoagulants
Concomitant administration of amoxicillin and anticoagulants from the coumarin class, may prolong the bleeding time. A dose adjustment of anticoagulants may be necessary.

Probenecid
By inhibiting the renal elimination of amoxicillin the concomitant administration of probenecid leads to an increase in the concentrations of amoxicillin in serum and bile.

Other antibiotics
In general amoxicillin should not be combined with bacteriostatic chemotherapeutics/antibiotics (like tetracyclines, macrolids, sulfonamids or chloramphenicol), because in vitro antagonism is observed. When used simultaneously with aminoglycosides a synergistic effect may occur.

Methotrexate
Interaction between amoxicillin and methotrexate leading to methotrexate toxicity has been reported. Serum methotrexate levels should be closely monitored in patients who receive amoxicillin and methotrexate simultaneously. Amoxicillin decreases the renal clearance of methotrexate, probably by competition at the common tubular secretion system.
Caution is recommended when amoxicillin is given concomitantly with:

Oral hormonal contraceptives
Administration of amoxicillin can transiently decrease the plasma level of estrogens and progesterone, and may reduce the efficacy of oral contraceptives. It is therefore recommended to take supplemental non-hormonal contraceptive measures.

Other forms of interactions:

- Forced diuresis leads to a reduction in blood concentrations by increased elimination of amoxicillin.
- The occurrence of diarrhoea may impair the absorption of other medicaments and consequently adversely affect the efficacy.
- It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.
- Amoxicillin may decrease the amount of urinary estriol in pregnant women.
- At high concentrations, amoxicillin may diminish the results of serum glycemia levels.
- Amoxicillin may interfere with protein testing when colormetric methods are used.

4.6 Pregnancy and lactation

Amoxicillin passes the placenta and foetal plasma concentrations are approximately 25-30% of the maternal plasma concentrations.
Data on a limited number of exposed pregnancies indicate no adverse effects of amoxicillin on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

Amoxicillin diffuses into the breast milk (approx. 10% of the corresponding serum concentration) and in rare cases this can lead to diarrhoea and/or fungal colonisation of the mucosa in the infant. The possibility of sensitisation of the infant to beta-lactam drugs should also be considered.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

In this section undesirable effects are defined as follows:
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
Uncommon
Superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis after prolonged and repeated use of amoxicillin.

Blood and the lymphatic system disorders
Rare
Eosinophilia and haemolytic anaemia.
Very rare
Leucopenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia, myelosuppression, agranulocytosis, prolongation of bleeding time, and prolongation of prothrombin time. All were reversible on discontinuation of therapy.

Immune system disorders
Rare
Laryngeal oedema, serum sickness, allergic vasculitis, anaphylaxis and anaphylactic shock.

Nervous system disorders
Rare
CNS effects including hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders:
Common
Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side effects can generally be reduced by taking amoxicillin during meals.
Rare
Superficial uperficial discoloration of the teeth (especially with the suspension). Usually the discoloration can be removed by teeth brushing.
Very rare
If severe and persistent diarrhoea occurs, the very rare possibility of pseudomembranous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.
Development of a black tongue.

Hepato-biliary disorders:
Uncommon
Moderate and transient increase of liver enzymes.
Rare
Hepatitis and cholestatic jaundice.

Skin and subcutaneous tissue disorders:
Common
Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5 - 11 days after start of therapy. Immediate appearance of urticaria indicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.
Rare (see also section 4.4)
Angioneurotic oedema (Quincke's oedema), erythema multiforme exsudativum, acute generalized pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis.

Renal disorders
Rare
Acute interstitial nephritis.

General disorders and administration site conditions
Rare
Drug fever.

4.9 Overdose

Symptoms of overdose:
Amoxicillin is not generally associated with acute toxic effects, even when accidentally consumed in high doses. Overdosage can lead to symptoms such as gastrointestinal disturbances and fluid and electrolyte imbalance. In patients with severely impaired renal function, large overdoses can result in signs of renal toxicity; crystalluria is possible.

Management of overdose:
There is no specific antidote for an overdose of amoxicillin.
Treatment consists primarily of administration of activated charcoal (a gastric lavage is usually not necessary) or symptomatic measures. Particular attention should be paid to the water and electrolyte balance of the patients. Amoxicillin can be eliminated via haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: J01CA04
Pharmacotherapeutic group: Beta-lactam antibacterials

Mode of action
Amoxicillin is an aminobenzyl penicillin that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

Mechanism of resistance
Bacteria may be resistant to amoxicillin (and, thus, ampicillin) due to production of beta-lactamases which hydrolyse aminopenicillins (hydrolysis which can be inhibited by clavulanic acid), due to alteration in penicillin-binding proteins, due to impermeability to the drug, or due to drug efflux pumps. One or more of these mechanisms may co-exist in the same organism, leading to a variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

Breakpoints (CLSI)
Enterobacteriaceae: S ≤ 8 µg/ml; I = 16 µg/ml; R ≥ 32 µg/ml
Staphylococcus spp.: S ≤ 4 µg/ml; R ≥ 8 µg/ml
Haemophilus spp.: S ≤ 1 µg/ml; R ≥ 4 µg/ml
Str. pneumoniae: S ≤ 2 µg/ml; I = 4 µg/ml; R ≥ 8 µg/ml

Susceptibility:
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
Bacillus anthracis
Listeria monocytogenes
Staphylococcus aureus (beta-lactamase negative, methicillin susceptible)
Streptococcus agalactiae
Streptococcus bovis
Streptococcus pyogenes *
Aerobic Gram-negative
Neisseria meningitidis
Anaerobes
Peptostreptococci
Species for which acquired resistance may be a problem
Aerobic Gram-positive
Corynebacterium spp
Enterococcus faecalis
Streptococcus pneumoniae * +
Streptococcus viridans
Aerobic Gram-negative
Haemophilus influenzae *
Haemophilus para-influenzae *
Neisseria gonorrhoea
Proteus mirabilis
Anaerobes
Bacteroides melaninogenicus
Fusobacterium spp
Inherently resistant organisms
Aerobic Gram-positive
Staphylococcus (β-lactamase producing strains)
Aerobic Gram-negative
Acinetobacter spp
Citrobacter spp
Enterobacter spp
Escherichia coli
Klebsiella spp
Moraxella catarrhalis *
Proteus spp (indol positive)
Proteus vulgaris
Providencia spp
Pseudomonas spp
Serratia spp
Anaerobes
Bacteroides fragilis
Others
Chlamydia
Mycoplasma
Rickettsia

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
+ Rates of resistance vary within Europe

5.2 Pharmacokinetic properties

Absorption:
The absolute bioavailability of amoxicillin depends on the dose and ranges between 75 and 90%. In the dose range between 250 mg and 750 mg the bioavailability (parameters: AUC and/or recovery in urine) is linearly proportional to the dose. At higher doses the extent of absorption decreases. The absorption is not affected by concomitant food intake. Oral administration of a single dose of 500 mg amoxicillin results in plasma concentrations of 6 - 11 mg/l. After administration of a single dose of 3 g amoxicillin, the plasmaconcentrations reach 27 mg/l. Peak plasma concentrations are present about 1-2 hours after administration.

Distribution:
Protein binding for amoxicillin is approximately 17%. Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. In healthy meninges amoxicillin diffuses badly in liquor cerebrospinalis. In inflamed meninges the concentration can reach approximately 20% of the concentration in blood. Amoxicillin crosses the placenta and a small percentage is excreted into the breast milk.

Biotransformation and elimination:
The main route of excretion of amoxicillin is the kidney. About 60-80% of an oral dose of amoxicillin are excreted in unchanged active form in the urine within 6 hours of administration, and a small fraction is excreted in the bile. Approximately 7 - 25% of the administered dose is metabolised to inactive penicilloic acid. The serum half-life in patients with normal renal function is approximately 1 – 1,5 hour. In patients with end-stage renal failure the half-life ranges between 5 to 20 hours. The substance is haemodialysable.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents:
Magnesium stearate
Cellulose, microcrystalline

Capsule Shell:
Yellow iron oxide (E-172)
Titanium dioxide (E-171)
Gelatin

Black printing ink:
Shellac
Soybean lecithin
Dimeticone
Black iron oxide (E-172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

48 months

6.4 Special precautions for storage

Do not store above 25 °C

6.5 Nature and contents of container

Nature: Blister consisting of a clear polyvinyl chloride foil with a coating of polyvinylidene chloride (PVC/PVDC) 236 µm and aluminium foil 20 µm.

Contents: Amoxicillin Sandoz 250 mg Capsules:
single packs for 12, 21 and 100 capsules
hospital packs for 500 and 1000 capsules

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

7 MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8 MARKETING AUTHORISATION NUMBER

PA 0111/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2001
Date of last renewal: 14 September 2005

10 DATE OF REVISION OF THE TEXT

July 2009