SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

PYROX COMBI

(Combipack of Rabeprazole Sodium Tablets 20 mg, Amoxicillin Tablets BP 1 gm, Clarithromycin Tablets USP 500 mg)

Amoxicillin Tablets BP

1.2. Strength

1 gm

1.3. Pharmaceutical Form

Solid Dosage form (Tablet)

2. Quality and Quantitative Composition

Qualitative Composition:

Each film coated tablet contains:

Amoxicillin Trihydrate BP Equivalent to

Amoxicillin	1 gm
Excipients	Q.S.

Colour: Sunset Yellow FCF

Sr. No.	Ingredients	Standard
1	Povidone	BP
2	Microcrystalline Cellulose	BP
3	Isopropyl Alcohol	BP
4	Purified Talc	BP
5	Magnesium Stearate	BP
6	Croscarmellose Sodium	BP
7	Insta coat ICS 1100 Orange	IH
8	Dichloromethane	BP

Quantitative Composition:

Each film coated tablet contains:

Amoxicillin Trihydrate BP Equivalent to

Amoxicillin 1 gm

Excipients Q.S.

Colour: Sunset Yellow FCF

Sr. No.	Ingredients	Standard	Quantity / Tablet
1	Povidone	BP	25.00 mg
2	Microcrystalline Cellulose	BP	30.00 mg
3	Isopropyl Alcohol	BP	0.25 ml
4	Purified Talc	BP	8.00 mg
5	Magnesium Stearate	BP	6.00 mg
6	Croscarmellose Sodium	BP	12.00 mg

7	Microcrystalline Cellulose	BP	9.00 mg
8	Insta coat ICS 1100 Orange	IH	44.00 mg
9	Isopropyl Alcohol	BP	0.33 ml
10	Dichloromethane	BP	0.50 ml

3. Pharmaceutical Form

Solid Dosage form (Tablet)

Orange coloured caplet shaped, biconvex, film coated tablets breakline on one side and other side plain.

4. Clinical Particulars

4.1 Therapeutic indications

Amoxicillin Tablets are indicated for the treatment of the following infections in adults and children.

- Acute bacterial sinusitis
- Acute Otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis
- Asymptomatic Bacteriuria in pregnancy
- Acute pyelonephritis
- Typhoid and paratyphoid fever
- Dental abscess with spreading cellulitis
- Prosthetic joint infections
- Helicobacter pylori eradication

• Lyme disease

Amoxicillin is also indicated for the prophylaxis of endocarditis

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

These Tablets are for oral administration.

Treatment of Infection: Adult dosage (including elderly patients):

Standard adult dosage: 250 mg three times daily, increasing to 500 mg three times daily for more severe infections.

High dosage therapy (maximum recommended oral dosage 6 g daily in divided doses): A dosage of 3 g twice daily is recommended in appropriate cases for the treatment of severe or recurrent purulent infection of the respiratory tract.

Short course therapy: Simple acute urinary tract infection: two 3 g doses with 10-12 hours between the doses. Dental abscess: two 3 g doses with 8 hours between the doses.

Gonorrhoea: single 3 g dose.

Helicobacter eradication in peptic (duodenal and gastric) ulcer disease:

Amoxicillin Tablets is recommended at a dose of twice daily in association with a proton pump inhibitor and antimicrobial agents as detailed below:

Omeprazole 40 mg daily, Amoxicillin 1G BID, Clarithromycin 500mg BID x 7days or Omeprazole 40mg daily, Amoxicillin750mg-1G BID, Metronidazole 400mg TID x 7 days.

Renal Impairment:

Glomerular filtration rate>30ml/min No adjustment necessary.

Glomerular filtration rate 10-30ml/min: Amoxicillin. max.500mg b.d.

Glomerular filtration rate<10ml/min: Amoxicillin. Max. 500mg/day.

4.3 Contraindications:

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients used.

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/hepatic impairment due to amoxicillin.

4.4 Special warnings and precautions for use:

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agencts.

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 and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders.

Renal impairment

In patients with renal impairment, the rate of excretion of amoxicillin will be reduced depending on the degree of impairment and it may be necessary to reduce the total daily unit amoxicillin dosage accordingly.

Skin reactions

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AEGP). This reaction requires amoxicillin discontinuation and contra-indicates any subsequent administration.

Amoxicillin 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.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease. It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease,

the spirochaete *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. 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 should immediately be discontinued, a physician consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported.

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. 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.

Crystalluria:

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.

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of amoxicillin may distort assay results for oestriol in pregnant women.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Allopurinol:

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Tetracyclines:

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitisation. 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. Amoxicillin should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Fertility:

There are no data on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

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 skin rash.

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin, presented 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)

- Blood and lymphatic system disorders: Very rarely Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia.
- Prolongation of bleeding time and prothrombin
- Immune system disorders: Very rarely severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis.
- If a hypersensitivity reaction is reported, the treatment must be discontinued.
- Nervous system disorders: Very rarely Hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

- Gastrointestinal disorders: Very rarely Antibiotic associated colitis including pseudomembraneous colitis and haemorrhagic colitis.
- Black hairy tongue
- Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.
- Skin and subcutaneous tissue disorders: Very rarely Skin reactions such as erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP)

Renal and urinary tract disorders: Very rarely interstitial nephritis, Crystalluria

4.9 Overdose

Symptoms and signs of overdose:

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) 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.

Treatment of intoxication:

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

Amoxicillin may be removed from the circulation by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: penicillins with extended spectrum; ATC code: J01C A04

Mechanism of action

Amoxicillin is 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.

Pharmacokinetic/pharmacodynamic 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 main mechanisms of resistance to amoxicillin are:

• Inactivation by bacterial beta-lactamases.

• 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.

5.2 Pharmacokinetic properties

Oral

Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (T_{max}) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers, are presented below.

C_{max}	T_{max}*	AUC $_{(0-24h)}$	T ½
(µg/ml)	(h)	((µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56
*Median (range)			

In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as C_{max} and AUC). The absorption is not influenced by simultaneous food intake.
Haemodialysis can be used for elimination of amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 l/kg.

Following intravenous administration, amoxicillin has 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. Amoxicillin, like most penicillin, can be detected in breast milk.

Amoxicillin has 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.

Elimination

The major route of elimination for amoxicillin is via the kidney.

Amoxicillin has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/hour in healthy subjects. Approximately 60 to 70% of the amoxicillin is excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of amoxicillin. Various studies have found the urinary excretion to be 50-85% for amoxicillin over a 24 hour period.

Concomitant use of probenecid delays amoxicillin excretion.

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/ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

Renal impairment

The total serum clearance of amoxicillin decreases proportionately with decreasing renal function.

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, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with amoxicillin.

6. 0 Pharmaceutical Particulars

6.1 List of excipients

Sr. No.	Ingredients	Standard
1	Povidone	BP
2	Microcrystalline Cellulose	BP
3	Isopropyl Alcohol	BP
4	Purified Talc	BP

5	Magnesium Stearate	BP
6	Croscarmellose Sodium	BP
7	Insta coat ICS 1100 Orange	IH
8	Dichloromethane	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C, protected from light.

Keep medicines out of reach of children.

6.5 Nature and contents of container

Carton for pyrox combi tablets (1 x 7 blisters)

6.6 Special precautions for disposal

No special requirements

7. Marketing Authorization Holder/ Registrant

Swiss Pharma Nig Ltd

8. Marketing Authorization Numbers

A4-9920

9. Date of first authorization/renewal of the authorization

27/05/2018

10. Date of revision of the text
