1.3 Product Information

1.3.1 Summary of Product Characteristics

Summary of product characteristic is attached.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Monuril 3 g granules for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 5.631 g of fosfomycin trometamol equivalent to 3.0 g fosfomycin

Excipients:
One sachet contains 2.213 g of sucrose, see section 4.4.
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Granules for oral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute lower uncomplicated urinary tract infections caused by pathogens sensitive to fosfomycin in women above 12 years of age.
Prophylaxis of urinary tract infections in surgical or diagnostic procedure involving lower urinary tract in adult males and females.

4.2 Posology and method of administration

The recommended dose for the treatment of acute uncomplicated lower urinary tract infections is a single Monuril 3 g sachet in women above 12 years of age.
The recommended regimen for the prophylaxis of urinary tract infections in surgery and diagnostic procedure involving lower urinary tract in adult males and females is one Monuril 3 g sachet 3 hours before surgery and one Monuril 3 g sachet 24 hours after surgery.

The safety and efficacy of Monuril 3 g in children below 12 years have not been established. No data are available.

Method of administration
Monuril 3g is for oral administration.
It should be taken on an empty stomach, preferably before bedtime, after emptying the bladder.
The dose should be dissolved into a glass of water or any other beverage, and taken immediately after its preparation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Patients with severe renal failure (creatinine clearance < 10 mL/min).
Patients undergoing haemodialysis.

4.4 Special warnings and precautions for use

Antibiotic associated colitis (incl. pseudomembranous colitis) has been reported in association with the use of broad spectrum antibiotics including fosfomycin trometamol; therefore it is important to

consider this diagnosis in patients who develop serious diarrhoea during or after the use of fosfomycin trometamol. In this situation adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

Food may delay the absorption of the active ingredient of Monuril 3g, with consequent slight decrease in peak plasma levels and urinary concentrations. It is therefore preferable to take the medicine on an empty stomach, about 2-3 hours after meals.

Monuril 3g contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Pediatric population
Experience in children with Monuril 3 g is limited. The product is not recommended for children below the age of 12.

4.5 Interaction with other medicinal products and other forms of interaction

When co-administered with fosfomycin, metoclopramide lowers the serum and urine concentrations of fosfomycin.
Other drugs that increase gastrointestinal motility may produce similar effects.

Pediatric population
Interaction studies have been performed only on adults.

4.6 Pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300 and 1000 pregnancy outcomes) indicate no malformative nor feto/ neonatal toxicity of fosfomycin trometamol.
Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of Monuril 3g may be considered during pregnancy, if necessary.

Lactation
It is unknown whether fosfomycin /fosfomycin metabolites are excreted in human milk.
A risk to the newborns/infants cannot be excluded.

4.7 Effects on ability to drive and use machines

Monuril 3g has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The most common adverse reactions following the single-dose administration of fosfomycin trometamol involve the gastrointestinal tract, mainly diarrhoea. These events are usually self-limited in duration and resolve spontaneously.
The following table displays ADRs that have been reported with the use of Monuril 3g from either clinical-trial or post-marketing experiences.

The displayed frequency categories use the following convention:
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 form the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reactions Frequency Category			
	Common (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (< 1/1,000)	**Not Known**
Infections and infestations	Vulvovaginitis			
Immune system disorders				Anaphylactic shock, Allergic reaction
Nervous system disorders	Headache, Dizziness	Paraesthesia		
Cardiac disorders			Tachycardia	
Respiratory, thoracic and mediastinal disorders				Asthma
Gastrointestinal disorders	Diarrhoea, Nausea, Dyspepsia	Abdominal pain, Vomiting		Psudomembranous colitis
Skin and subcutaneous tissue disorders		Rash, Urticaria, Pruritus		Angioedema
General disorders and administration site conditions		Fatigue		
Vascular Disorders				Hypotension

4.9 Overdose

The following events have been observed in patients who have taken Monuril 3g in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception.

In the event of overdosage, treatment should be symptomatic and supportive.
The patient should drink large quantities of water to promote urinary elimination of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use – other antibacterials ATC code: J01XX01

Monuril 3g contains fosfomycin tromethamine salt, a broad-spectrum, bactericidal antibiotic. It acts on at the first stage of bacterial wall synthesis. Being an analogue of phosphoenolpyruvate, it inhibits the phosphoenolpyruvate transferase enzyme, thereby irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps in bacterial cell wall synthesis. It can also reduce bacterial adhesion to bladder mucosa, which can be a predisposing factor for recurring infections. Its mechanism of action explains the lack of cross-resistance with other antibiotics and the synergism with other classes of antibiotics, such as beta-lactam antibiotics.

Fosfomycin-trometamol acts against a broad range of Gram-positive and Gram-negative microorganisms commonly isolated in urinary tract infections, such as E.coli, Citrobacter spp., Klebsiella spp., Proteus spp., Serratia spp., P. aeruginosa and Enterococcus faecalis.

The emergence of *in vitro* resistance occurs as a mutation of the chromosomal genes glpT and uhp, which control the transport of L-alpha-glycerophosphate and hexose phosphate, respectively.

5.2 Pharmacokinetic properties

Absorption
After oral administration, fosfomycin is well absorbed from the gut and has an absolute bioavailability of about 50%. Food delays absorption, not influencing urinary concentrations.

Distribution
Fosfomycin is distributed to the kidneys, bladder wall, prostate and seminal vesicles. Sustained concentrations of fosfomycin higher than the minimum inhibitory concentrations (MIC) are obtained in urine for 24-48 hours after oral administration.
Fosfomycin is not bound to plasma proteins and crosses the placental barrier.

Elimination
Fosfomycin is excreted unchanged mainly via the kidneys by glomerular filtration (40-50% of the dose is found in the urine) with an elimination half-life of about 4 hours and to a lesser extent in feces (18-28% of the dose). The appearance of a second serum peak 6 and 10 hours after drug intake suggests that the drug is subject to enterohepatic recirculation.

The pharmacokinetic features of fosfomycin are not modified by age or pregnancy. The drug accumulates in patients with renal failure; linear relationships have been established between fosfomycin pharmacokinetic parameters and glomerular filtration rate data.

5.3 Preclinical safety data

In acute toxicity studies a single oral dose of 5000 mg/kg was well tolerated both in mice and rats and a single dose of 2000 mg/kg did not produce changes in rabbits and dogs.

Repeated dose studies by oral route showed that the no-effect dose was between 100 and 200 mg/kg after 4 weeks of treatment in dogs and rats, respectively.

Genotoxicity studies have shown that fosfomycin is devoid of mutagenic potential.

Reproductive and development toxicity studies have not disclosed any teratogenic effects, any signs of peri- and postnatal toxicity or any untoward effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mandarin flavour
Orange flavour
Saccharin
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C in the original package.

6.5 Nature and contents of container

Sachets are a four layer laminate: paper, polyethylene, aluminium, polyethylene.
Sachets are supplied in cardboard outer containing 1 sachet.

6.6 Special precautions for disposal and other handling

The dose must be dissolved in a glass of water and administered soon after dissolving.

Any unused product or waste material should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zambon S.p.A.
via Lillo del duca,10
20091-Bresso
Milan
Italy

8. MARKETING AUTHORISATION NUMBER(S)

NAFDAC Reg. N°: B4-4173

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1.3.2 Labelling (outer & inner labels)

Please find the artworks of Monuril attached.

Zambon 1906

Draft 4

H15Y700	E02.0818	CYAN C	1/2
H15Y700	E02.0818	390 C	2/2

A2
A3
A4

Monuril® 3 g

granules for oral solution

FOSFOMYCIN TROMETAMOL

B1
B2
B3
B4

Manufacturer: Zambon Switzerland Ltd., Via Industria 13, CH-6814 Cadempino – Switzerland

Imported and Distributed By: Phillips Pharmaceuticals (Nigeria) Ltd, Afprint Industrial Estate, Plot 122-132, Apapa Oshodi Expressway, Lagos, Nigeria

NAFDAC REG. NO: B4-4173

Zambon

Monuril® 3 g

granules for oral solution

E02.0818

Each 8 g sachet contains:
5.631 g of fosfomycin trometamol equivalent to 3.0 g fosfomycin, mandarin flavour, orange flavour, saccharin, sucrose (2.213 g per sachet)

H15Y700

READ CAREFULLY THE PACKAGE LEAFLET BEFORE USE.
STORE BELOW 30°C IN THE ORIGINAL PACKAGE.
KEEP OUT OF THE REACH OF CHILDREN.

Preparation:
The content of a sachet should be dissolved in a glass of water and taken immediately.

MEDICINAL PRODUCT SUBJECT TO MEDICAL PRESCRIPTION

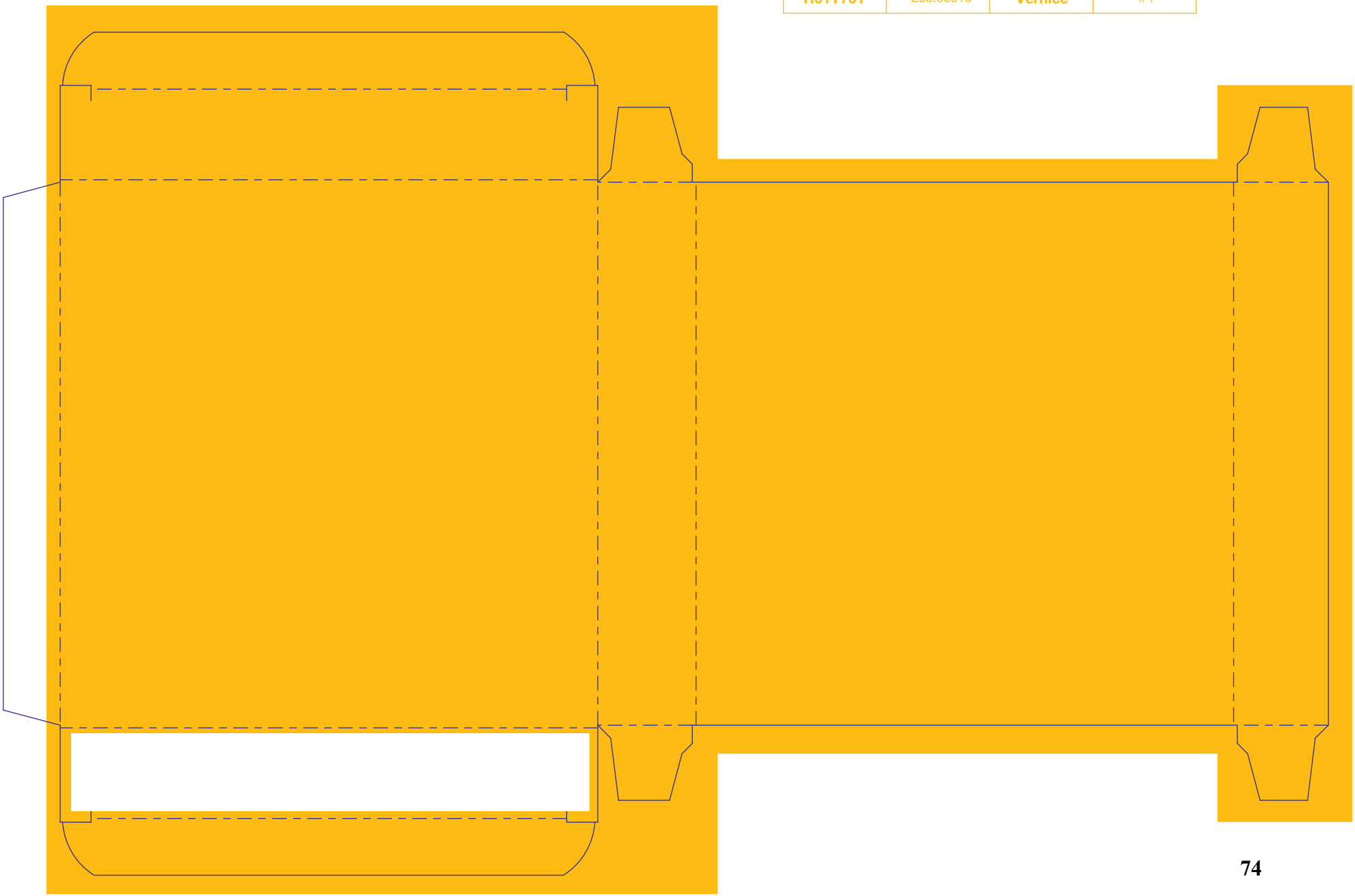
A1 Batch n.: Mfd.: Exp. date:

Draft 8

FUSTELLA		AS 1076 2C-B	104x19x105
H01Y701	E03.0818	CYAN	1/4
H01Y701	E03.0818	BLACK	2/4
H01Y701	E03.0818	390 C	3/4
H01Y701	E03.0818	Vernice	4/4

Retinatura 40%

H01Y701	E03.00818	Vernice	4/4



1.3.3 Packaging Insert (also known as patient information PIL)

Pack insert of Monuril is enclosed.

Draft 4

H02Y701	E02.0818	425 U	FI 502: 135x210 mm	1/1B	Retinatura 40%

Monuril® 3g, granules for oral solution

Fosfomycin trometamol

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Monuril is and what it is used for

The active substance contained in Monuril 3g granules for oral solution is fosfomycin trometamol which belongs to a group of antibiotics used to treat infections.

Monuril 3g granules for oral solution is used for treatment of acute lower uncomplicated urinary tract infections caused by pathogens sensitive to fosfomycin in women above 12 years of age.
Prophylaxis of urinary tract infections in surgical or diagnostic procedure involving lower urinary tract in adult males and females.

2. Before you use Monuril

Do not use Monuril
- If you are allergic to fosfomycin trometamol or any of the other ingredients of Monuril (see section 6 "Further Information");
- If your kidney function is impaired (creatinine's clearance is < 10 ml/min).
- If you are undergoing haemodialysis.

Take special care with Monuril

Meals may delay the absorption of the active ingredient causing a slight decrease in blood peak and urine levels.
You may develop **diarrhoea** whilst taking, or after taking, antibiotics including Monuril. If this becomes severe or persistent or you notice that your stool contains blood or mucus consult your doctor immediately. Do not treat diarrhoea without first checking with your doctor.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is especially important if you take metoclopramide or other drugs that increase the movement of food through the stomach and intestines during the treatment with Monuril, as absorption of Monuril could be reduced.

Using Monuril with food and drink

Take Monuril on an empty stomach (2-3 hours after the meal), preferably before bedtime, just after emptying the bladder. If you take Monuril during meals, its absorption can be delayed.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, contact your doctor before using Monuril. Your doctor will decide if you can take this medicine.

Driving and using machines

Monuril has no influence on the ability to drive and use machines.

Important information about some of the ingredients of Monuril 3g granules for oral solution

Monuril 3g granules contains 2.213 g of sucrose: if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to use Monuril

Always use Monuril exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- The usual dose for adults is 1 sachet of

Monuril 3g granules for oral solution 1 time a day. **Do not use more than one single dose / sachet to treat a single episode of acute cystitis.**
- The recommended regimen for the prophylaxis of urinary tract infections in surgery and diagnostic procedure involving lower urinary tract in adult males and females is 1 sachet of Monuril 3 g granules for oral solution 3 hours before surgery and 1 sachet 24 hours after surgery.
- Dissolve the content of one sachet in a glass of water (50-100 ml) and drink immediately.

Monuril should be taken on an empty stomach (2-3 hours after the meal), preferably before going to bed, after emptying the bladder.

This product is not recommended for use in children.

V **If you take more Monuril than you should**, consult your physician or pharmacist immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Monuril can cause side effects, although not everybody gets them.
R The side effects are mentioned below and are arranged by frequency of occurrence.
The frequencies are defined as:
Very common: may affect more than 1 in 10 people; Common: may affect up to 1 in 10 people; Uncommon: may affect up to 1 in 100 people; Rare: may affect up to 1 in 1,000 people; Very rare: may affect up to 1 in 10,000 people; Not known: frequency cannot be estimated from the available data.

The most common adverse reactions following the single-dose administration of fosfomycin trometamol involve the gastrointestinal tract, mainly diarrhoea. These events are usually self-limited in duration and resolve spontaneously.

Common:
- Headache, Dizziness
- Diarrhoea - if it becomes **severe** consult your doctor **immediately** (see also section "Take special care"), Nausea, Indigestion (dyspepsia)
- Inflammation of the vagina and vulva (vulvo-vaginitis)

Uncommon:
- Weakness (asthenia)
- Paraesthesia
- Abdominal pain, Vomiting
- Rash, Urticaria, Pruritus

Rare:
- Tachycardia

Unknown:
- Asthma
- Anaphylactic shock, Allergic reaction
- Pseudomembranous colitis
- Angioedema
- Hypotension.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Monuril
Keep out of the reach and sight of children.

Do not use Monuril after the expiry date which is stated on the carton or sachet.
Store below 30°C in the original package.

V

6. Further information
What does Monuril contains
- Each sachet contains 5.631 g of fosfomycin trometamol equivalent to 3.0 g fosfomycin.
- The other ingredients are: mandarin flavour, orange flavour, saccharin, sucrose (2.213 g per sachet).

What Monuril looks like and contents of the pack R
Monuril 3g granules for oral solution are white granules for oral solution, with a characteristic mandarin flavour.
Monuril 3g granules for oral solution are packed in paper/polyethylene/aluminium/polyethylene sachet, containing 8g of granulate; 1 sachet per box.

Manufacturer:
Zambon Switzerland Ltd., Via Industria 13,
CH-6814 Cadempino – Switzerland

Imported and distributed By:
Phillips Pharmaceuticals (Nigeria) Ltd, Afprint Industrial Estate, Plot 122-132, Apapa Oshodi Expressway, Lagos, Nigeria

NAFDAC Reg. N°: B4-4173