For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

SUPACEF 250 mg/750 mg/1.5 g

1. GENERIC NAME

Cefuroxime Sodium Injection IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Cefuroxime Sodium IP equivalent to Cefuroxime 250 mg/750 mg/1.5 g

List of Excipients

None.

3. DOSAGE FORM AND STRENGTH

Powder for solution for injection.

Each vial contains:
Cefuroxime Sodium IP equivalent to Cefuroxime 250 mg/750 mg/1.5 g

4. CLINICAL PARTICULARS

4.1. Therapeutic Indication

SUPACEF is a bactericidal cephalosporin antibiotic which is resistant to most beta-lactamases and is active against a wide range of Gram-positive and Gram-negative organisms.

It is indicated for the treatment of infections before the infecting organism has been identified or when caused by sensitive bacteria. Susceptibility to *SUPACEF* will vary with geography and time and local susceptibility data should be consulted where available *(see 5 Pharmacological Properties, 5.2 Pharmacodynamic Properties*).

Indications include:
- respiratory tract infections for example, acute exacerbation of chronic bronchitis, infected bronchiectasis, bacterial pneumonia, lung abscess and post-operative chest infections
- ear, nose and throat infections for example, sinusitis, tonsillitis, pharyngitis and otitis media
- urinary tract infections for example, acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria
- soft-tissue infections for example, cellulitis, erysipelas and wound infections
- bone and joint infections for example, osteomyelitis and septic arthritis
- obstetric and gynaecological infections, pelvic inflammatory diseases
- gonorrhoea particularly when penicillin is unsuitable
- other infections including septicaemia, meningitis
- prophylaxis against infection in abdominal, pelvic, orthopaedic, cardiac, pulmonary, oesophageal and vascular surgery where there is increased risk from infection.

Usually *SUPACEF* will be effective alone, but when appropriate it may be used in combination with an aminoglycoside antibiotic, or in conjunction with metronidazole (orally or by suppository or injection), especially for prophylaxis in colonic or gynaecological surgery.

Where appropriate *SUPACEF* is effective when used prior to oral therapy with *CEFTUM* (cefuroxime axetil) in the treatment of pneumonia and acute exacerbations of chronic bronchitis.

4.2. Posology and Method of Administration

SUPACEF Injection is for intravenous (i.v.) and/or intramuscular (i.m.) administration only.

SUPACEF is also available as the axetil ester (*CEFTUM*) for oral administration. This permits the use of sequential therapy with the same antibiotic, when a change from parenteral to oral therapy is clinically indicated.

No more than 750 mg should be injected at one intramuscular site.

General Dosing Recommendations

- *Adults*

Many infections respond to 750mg three times daily by i.m. or i.v. injection. For more severe infections the dose should be increased to 1.5g three times daily given i.v. The frequency of administration may be increased to 6-hourly if necessary, giving total daily doses of 3 to 6 g. Where clinically indicated, some infections respond to 750mg or 1.5g twice daily (i.v. or i.m.) followed by oral therapy with *CEFTUM*.

- *Infants and Children*

30 to 100 mg/kg/day given as 3 or 4 divided doses. A dose of 60mg/kg/day is appropriate for most infections.

- *Neonates*

30 to 100 mg/kg/day given as 2 or 3 divided doses. (*see 5.3 Pharmacokinetic Properties*).

Gonorrhoea

- *Adults*

1.5g as a single dose (as 2 x 750 mg injections given i.m. with different sites, e.g. each buttock).

Meningitis

SUPACEF is suitable for sole therapy of bacterial meningitis due to sensitive strains.

Populations

- *Adults:* - 3g given i.v. every 8 hours
- *Infants and Children:* - 150 to 250 mg/kg/day given i.v. in 3 or 4 divided doses

- *Neonates:* - the dosage should be 100 mg/kg/day given i.v.

Prophylaxis

Polulations

- *Adults*

The usual dose is 1.5 g given i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations. This may be supplemented with two 750 mg i.m. doses 8 and 16 hours later.

In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1.5 g given i.v. with induction of anaesthesia, continuing with 750 mg given i.m. three times daily for a further 24 to 48 hours.

In total joint replacement, 1.5 g *SUPACEF* powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.

Sequential Therapy

Populations

- *Adults*

Duration of both parenteral and oral therapy is determined by the severity of the infection and the clinical status of the patient.

Pneumonia

1.5 g *SUPACEF* three times daily or twice daily (given i.v. or i.m.) for 48 to 72 hours, followed by 500 mg twice daily *CEFTUM* (cefuroxime axetil) oral therapy for 7 to 10 days.

Acute Exacerbations of Chronic Bronchitis

750 mg *SUPACEF* three times daily or twice daily (given i.v. or i.m.) for 48 to72 hours, followed by 500 mg twice daily *CEFTUM* (cefuroxime axetil) oral therapy for 5 to 10 days.

Renal Impairment

Cefuroxime is excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of *SUPACEF* should be reduced to compensate for its slower excretion.

It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily) until the creatinine clearance falls to 20ml/min or below.

In adults with marked impairment (creatinine clearance 10 to 20 ml/min) 750 mg twice daily is recommended and with severe impairment (creatinine clearance <10 ml/min) 750 mg once daily is adequate.

For patients on haemodialysis a further 750 mg dose should be given i.v. or i.m. at the end of each dialysis. In addition to parenteral use, *SUPACEF* can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 litres of dialysis fluid).

For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units a suitable dosage is 750 mg twice daily. For low-flux haemofiltration follow the dosage recommended under impaired renal function.

4.3. Contraindications

Hypersensitivity to cephalosporin antibiotics.

4.4. Special Warnings and Precautions for Use

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see Section 4.8 Undesirable effects.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides, as renal impairment has been reported with these combinations. Renal function should be monitored in these patients, the elderly, and those with pre-existing renal impairment (*see 4.2 Posology and Method of Administration).*

As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few paediatric patients treated with *SUPACEF*. Persistence of positive cerebral spinal fluid (CSF) cultures of *Haemophilus influenzae* at 18-36 hours has also been noted with *SUPACEF* injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

As with other antibiotics, use of *SUPACEF* may result in the overgrowth of *Candida.* Prolonged use may also result in the overgrowth of other non-susceptible organisms (e.g. enterococci and *Clostridioides difficile*), which may require interruption of treatment.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Intracameral use and ocular toxicity

Serious ocular toxicity, including corneal opacity, retinal toxicity and visual impairment has been reported following off-label intracameral use of *SUPACEF*. *SUPACEF* should not be administered intracamerally.

With a sequential therapy regime, the timing of change to oral therapy is determined by severity of the infection, clinical status of the patient and susceptibility of the pathogens involved. If there is no clinical improvement within 72 hours, then the parenteral course of treatment must be continued.

Refer to the relevant prescribing information for *CEFTUM* before initiating sequential therapy.

4.5. Drug Interactions

In common with other antibiotics, *SUPACEF* may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

SUPACEF does not interfere in enzyme-based tests for glycosuria.

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false - positive results, as may be experienced with some other cephalosporins.
It is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving *SUPACEF*.

This antibiotic does not interfere in the alkaline picrate assay for creatinine.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

- *Infants and Children*

30 to 100 mg/kg/day given as 3 or 4 divided doses. A dose of 60 mg/kg/day is appropriate for most infections.

- *Neonates*

30 to 100 mg/kg/day given as 2 or 3 divided doses. (*see 5.3 Pharmacokinetic Properties*).

Gonorrhoea

- *Adults*

1.5g as a single dose (as 2 x 750 mg injections given i.m. with different sites, e.g. each buttock).

Meningitis

SUPACEF is suitable for sole therapy of bacterial meningitis due to sensitive strains.

- *Adults:* - 3g given i.v. every 8 hours
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- *Neonates:* - the dosage should be 100 mg/kg/day given i.v.

Prophylaxis

The usual dose is 1.5 g given i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations. This may be supplemented with two 750 mg i.m. doses 8 and 16 hours later.

In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1.5 g given i.v. with induction of anaesthesia, continuing with 750 mg given i.m. three times daily for a further 24 to 48 hours.

In total joint replacement, 1.5 g *SUPACEF* powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.

Sequential Therapy

- *Adults*

Duration of both parenteral and oral therapy is determined by the severity of the infection and the clinical status of the patient.

Pneumonia

1.5 g *SUPACEF* three times daily or twice daily (given i.v. or i.m.) for 48 to 72 hours, followed by 500 mg twice daily *CEFTUM* (cefuroxime axetil) oral therapy for 7 to 10 days.

Acute Exacerbations of Chronic Bronchitis

750 mg *SUPACEF* three times daily or twice daily (given i.v. or i.m.) for 48 to72 hours, followed by 500 mg twice daily *CEFTUM* (cefuroxime axetil) oral therapy for 5 to 10 days.

Renal Impairment

Cefuroxime is excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of *SUPACEF* should be reduced to compensate for its slower excretion.

It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily) until the creatinine clearance falls to 20 ml/min or below.

In adults with marked impairment (creatinine clearance 10 to 20ml/min) 750 mg twice daily is recommended and with severe impairment (creatinine clearance <10 ml/min) 750 mg once daily is adequate.

For patients on haemodialysis a further 750 mg dose should be given i.v. or i.m. at the end of each dialysis. In addition to parenteral use, *SUPACEF* can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 litres of dialysis fluid).

For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units a suitable dosage is 750 mg twice daily. For low-flux haemofiltration follow the dosage recommended under impaired renal function.

Pregnancy and Lactation

There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime, but, as with all drugs, it should be administered with caution during the early months of pregnancy. Cefuroxime is excreted in human milk, and consequently caution should be exercised when *SUPACEF* is administered to a nursing mother.

4.7. Effects on Ability to Drive and Use Machines

None reported.

4.8. Undesirable Effects

Adverse drug reactions are very rare (<1/10,000) and are generally mild and transient in nature.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition, the incidence of adverse reactions associated with *SUPACEF* may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:

Very common ≥1/10,
Common ≥1/100 to <1/10,
Uncommon ≥1/1000 to <1/100,
Rare ≥1/10,000 to <1/1000,
Very rare <1/10,000.

Infections and infestations

Rare	Candida overgrowth

Blood and lymphatic system disorders

Common	Neutropenia, eosinophilia.
Uncommon	Leukopenia, decreased haemoglobin concentration**,** positive Coomb's test.
Rare	Thrombocytopenia.
Very rare	Haemolytic anaemia.

Cephalosporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug to produce a positive Coomb's Test (which can interfere with cross matching of blood) and very rarely haemolytic anaemia.

Immune system disorders

Hypersensitivity reactions including

Uncommon	Skin rash, urticaria and pruritus**.**
Rare	Drug fever.
Very rare	Interstitial nephritis, anaphylaxis, cutaneous vasculitis.

See also Skin and subcutaneous tissue disorders and Renal and urinary disorders.

Cardiac disorders

Very rare Kounis syndrome

Gastrointestinal disorders

Uncommon	Gastrointestinal disturbance.
Very rare	Pseudomembranous colitis *(see 4.4 Special Warnings and Precautions for Use)*.

Hepatobiliary disorders

Common	Transient rise in liver enzymes.
Uncommon	Transient rise in bilirubin.

Transient rises in serum liver enzymes or bilirubin occur, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver.

Skin and subcutaneous tissue disorders

Very rare	Erythema multiforme, toxic epidermal necrolysis and Stevens Johnson Syndrome.

See also Immune system disorders.

Renal and urinary disorders

Very rare	Elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance *(see 4.4 Special Warnings and Precautions for Use).*

See also Immune system disorders.

General disorders and administration site conditions

Common	Injection site reactions which may include pain and thrombophlebitis

Pain at the intramuscular injection site is more likely at higher doses. However, it is unlikely to be a cause for discontinuation of treatment.

4.9. Overdose

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of Action

Cefuroxime is a well characterised and effective antibacterial agent which has bactericidal activity against a wide range of common pathogens, including β-lactamase producing strains. Cefuroxime has

good stability to bacterial β-lactamase, and consequently is active against many ampicillin-resistant or amoxycillin-resistant strains.

The bactericidal action of cefuroxime results from inhibition of cell wall synthesis by binding to essential target proteins.

5.2. Pharmacodynamic Properties

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

***In vitro* susceptibility of micro-organisms to Cefuroxime** Where clinical efficacy of cefuroxime has been demonstrated in clinical trials this is indicated with an asterisk (*).
Commonly Susceptible Species
Gram-Positive Aerobes: *Staphylococcus aureus* (methicillin susceptible)* *Coagulase negative staphylococcus* (methicillin susceptible) *Streptococcus pyogenes** Beta-hemolytic streptococci
Gram-Negative Aerobes: *Haemophilus influenzae* including ampicillin resistant strains* *Haemophilus parainfluenzae** *Moraxella catarrhalis** *Neisseria gonorrhoea** including penicillinase and non-penicillinase producing strains *Neisseria meningitidis* *Shigella* spp.
Gram-Positive Anaerobes: *Peptostreptococcus* spp. *Propionibacterium* spp.
Spirochetes: *Borrelia burgdorferi**
Organisms for which acquired resistance may be a problem
Gram-Positive Aerobes: *Streptococcus pneumoniae** Viridans group streptococcus
Gram-Negative Aerobes: *Bordetella pertussis* *Citrobacter* spp. not including *C. freundii* *Enterobacter* spp. not including *E. aerogenes* and *E. cloacae* *Escherichia coli** *Klebsiella* spp. including *K. pneumoniae** *Proteus mirabilis* *Proteus* spp. not including *P. penneri* and *P. vulgaris* *Providencia* spp. *Salmonella* spp.
Gram-Positive Anaerobes: *Clostridium* spp.

Gram-Negative Anaerobes: *Bacteroides* spp. not including *B. fragilis* *Fusobacterium* spp.
Inherently resistant organisms
Gram-Positive Aerobes: *Enterococcus* spp. including *E. faecalis* and *E. faecium* *Listeria monocytogenes*
Gram-Negative Aerobes: *Acinetobacter* spp. *Burkholderia cepacia* *Campylobacter* spp. *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Morganella morganii* *Proteus penneri* *Proteus vulgaris* *Pseudomonas* spp. including *P. aeruginosa* *Serratia* spp. *Stenotrophomonas maltophilia*
Gram-Positive Anaerobes: *Clostridioides difficile*
Gram-Negative Anaerobes: *Bacteroides fragilis*
Others: *Chlamydia* species *Mycoplasma* species *Legionella* species

5.3. Pharmacokinetic Properties

Absorption

Peak levels of cefuroxime are achieved within 30 to 45 minutes after i.m. administration.

Distribution

Protein binding has been variously stated as 33 - 50% depending on the methodology used.

Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in bone, synovial fluid and aqueous humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Metabolism

Cefuroxime is not metabolised and is excreted by glomerular filtration and tubular secretion.

Elimination

The serum half-life after either i.m. or i.v. injection is approximately 70 minutes.

In the first weeks of life the serum half-life of cefuroxime can be 3 to 5 times that in the adult.

Concurrent administration of probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level.

There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration. The major part is excreted in the first 6 hours.

Serum levels of cefuroxime are reduced by dialysis.

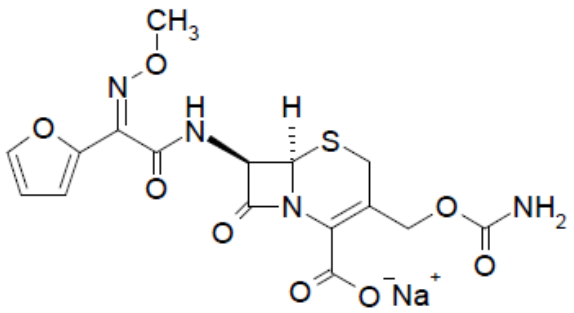
6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology

No additional data of relevance.

7. DESCRIPTION

It is the sodium salt of (Z)-3-Carbamoyloxymethyl-7-[2-(2-furyl)-2-methoxyimino-acetamido]-3-cephem-4- carboxylic acid, sodium salt, and it has the following chemical structure:



The empirical formula is $C_{16}H_{15}N_4NaO_8S$, representing a molecular weight of 446.4.

Cefuroxime Sodium is a white to cream powder to which appropriate amounts of water are added to prepare an off-white suspension for intramuscular use or a yellowish solution for intravenous use.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

SUPACEF should not be mixed in the syringe with aminoglycoside antibiotics.

The pH of 2.74% w/v Sodium Bicarbonate Injection considerably affects the colour of the solution and therefore this solution is not recommended for the dilution of *SUPACEF*. However, if required, for patients receiving Sodium Bicarbonate Injection by infusion *SUPACEF* may be introduced into the tube of the giving set.

8.2. Shelf-Life

24 months.

The expiry date of the powder is indicated on the label and packaging.

Shelf life after reconstitution and dilution under controlled and validated aseptic conditions:

Suspension and solution for Injection - 5 hours below 25° C or 72 hours at 2 to 8° C

Solution for Infusion –. Use immediately or within 24 hours at 2 to 8°C.

Shelf life if reconstitution and dilution has not taken place in controlled and validated aseptic conditions:

The product should be used immediately or within 24 hours if stored at 2 to 8° C.

8.3. Packaging Information

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

Some increase in the colour of prepared solutions and suspensions of *SUPACEF* may occur on storage.

Keep out of reach of children.

Nature and Specification of Container

Type I or III glass vials with bromobutyl or fluoro-resin laminated butyl rubber plugs and flip-off type overseals.

All pack presentations may not be marketed in the country.

8.4. Storage and Handling Instructions

Intramuscular

Add 1 ml Sterile Water for Injection to 250 mg *SUPACEF* or 3 ml Sterile Water for Injection to 750 mg *SUPACEF*. Shake gently to produce an opaque suspension.

Intravenous

Dissolve *SUPACEF* in Sterile Water for Injection using at least 2 ml for 250 mg, at least 6 ml for 750 mg, or 15 ml for 1.5 g. Shake gently to produce a yellowish solution.

Intravenous infusion

Dissolve 1.5 g of *SUPACEF* in 15 ml of Sterile Water for Injection. Add the reconstituted solution of *SUPACEF* to 50 or 100 ml of a compatible infusion fluid *(see information on Compatibility below)* These solutions may be given directly into the vein or introduced into the tubing of the giving set if the patient is receiving parenteral fluids.

Compatibility

1.5 g *SUPACEF* constituted with 15ml Water for Injections may be added to metronidazole injection (500 mg/100 ml).

1.5 g *SUPACEF* is compatible with azlocillin 1g (in 15 ml) or 5 g (in 50 ml).

SUPACEF (5 mg/ml) is compatible with 5% w/v or 10% w/v xylitol injection.

SUPACEF may be constituted for i.m. use with aqueous solutions containing up to 1% lidocaine hydrochloride.

SUPACEF is compatible with the following more commonly used i.v. infusion fluids.

Sodium Chloride Injection 0.9% w/v
5% Dextrose Injection
0.18% w/v Sodium Chloride plus 4% Dextrose Injection
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose and 0.45% Sodium Chloride Injection
5% Dextrose and 0.225% Sodium Chloride Injection
10% Dextrose Injection
10% Invert Sugar in Water for Injection
Ringer's Injection
Lactated Ringer's Injection
M/6 Sodium Lactate Injection
Compound Sodium Lactate Injection (Hartmann's Solution).

The stability of *SUPACEF* in Sodium Chloride Injection 0.9% w/v and in 5% Dextrose Injection is not affected by the presence of hydrocortisone sodium phosphate.

SUPACEF has also been found compatible admixed in i.v. infusion with: Heparin (10 and 50 units/ml) in 0.9% Sodium Chloride Injection; Potassium Chloride (10 and 40 mEqL) in 0.9% Sodium Chloride Injection.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or their patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *SUPACEF*. Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

Manufactured by:
ACS Dobfar S.p.A.,
via Alessandro Fleming, 2,
37135 Verona, Italy.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

12-73/80-DC dated 6th June 1988

12. DATE OF REVISION

23-Apr-2024

Trade marks are owned by or licensed to the GSK group of companies.

Version SUP/PI/IN/2024/01

Adapted from ZINACEF PDS 02 dated 11 August 2023