IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0361/030/002
Case No: 2042214

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

Martindale Pharmaceuticals Ltd

Bampton Road, **Harold Hill**, **Romford**, **RM3 8UG**, **United Kingdom**

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

Cefuroxime Martindale Pharma 1.5g powder for solution for Injection

the particulars of which are set out in 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 **18/06/2010** until **17/06/2015**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefuroxime Martindale Pharma 1.5g powder for solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1500 mg Cefuroxime (as 1578 mg cefuroxime Sodium).

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Powder for Solution for Injection.
White to almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefuroxime is indicated in the parenteral treatment of the following infections caused by organisms that are sensitive to cefuroxime:

Lower respiratory tract infections: acute exacerbation of chronic bronchitis and bacterial pneumonia

Upper urinary tract infections: pyelonephritis.

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

4.2 Posology and method of administration

Usual dosage:
Adolescents (age 12 to 17 years), adults and elderly

Most infections will respond to cefuroxime 750 mg three times a day.

For more severe infections, the dose may be increased to 1.5 g three times a day by intravenous injection.
If necessary, the frequency of administration of cefuroxime can be increased to four times a day 750 mg up to total daily doses of 3 g or four times a day 1500 mg up to total daily doses of 6 g.

Dosage in impaired renal function for adolescents, adults and elderly:
It is not necessary to reduce the dose if creatinine clearance is more than 20 ml/min.

In patients with markedly impaired renal function the dosage of cefuroxime should be reduced as follows:

Creatinine clearance (ml/min)	Recommended dosage of cefuroxime (mg)	Frequency of dosage (hours)
> 20	normal dosage	
10-20	750	12
< 10	750	24
Patients on continous	750	12

arteriovenous haemofiltration/haemo-dialysis		

Special precautions are required if creatinine clearance is <10 ml/minute and treatment should take place under appropriate expert supervision (see section 4.4).
Serum concentration of cefuroxime should be monitored in patients with severe renal impairment.
For patients on haemodialysis a further 750mg dose, by intravenous or intramuscular injection, should be given at the end of each session.

For low- flux haemofiltration follow the dosage recommended under impaired renal function.

Paediatric patients

Preterm (born at <36 weeks of gestation) and term newborn infants (age 0-27 days):
Cefuroxime is not recommended for the use in these age groups due to insufficient data on safety and efficacy. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults (see section 5.2).

Infants, toddlers (age 28 days to 23 months) and Children (2 years to 11 years):
The recommended dosage range is 30 to 100 mg/kg/day given as three or four divided doses. Most infections will respond to a dose of 60 mg/kg/day.

Infants, toddlers (28 days to 23 months) and children (2 to 11 years) with impaired renal function:
There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended.

In case of paediatric dose where use of 1.5g vial is not appropriate, consideration should be given to the use of a 750 or 250mg vial.

Route of Administration:

Cefuroxime may be administered by intravenous injection (within 3 – 5 minutes) (see section 6.6).

Doses above 750 mg of cefuroxime should not be administered intramuscularly.

4.3 Contraindications

Hypersensitivity to cefuroxime or to any other cephalosporin antibiotics.

Previous immediate and /or severe hypersensitivity reaction to penicillin or any beta-lactam drug.

4.4 Special warnings and precautions for use

Special care is indicated in patients who have experienced an allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

If severe hypersensitivity reactions or anaphylactic reactions occur after administration of cefuroxime sodium, the use of Cefuroxime should be discontinued immediately and appropriate emergency measures should be initiated.

In patients who develop severe diarrhoea during or after use of cefuroxime sodium, the risk of life threatening pseudo-membranous colitis should be taken into account. The use of cefuroxime sodium should be discontinued and appropriate treatment measures should be established. The use of preparations inhibiting the intestinal peristaltic is contra-indicated (see section 4.8).

As with other broad spectrum antibiotics, prolonged use of Cefuroxime sodium may result in the overgrowth of non-susceptible organisms (e.g., candida, enterococci and clostridium difficile), which may require interruption of treatment.

Cefuroxime is excreted via the kidneys. Therefore a dose adjustment is required in patients with impaired renal function (see section 4.2).
Due to an increased risk of cefuroxime accumulation in serum accompanied by an increased risk for undesirable effects patients with a creatinine clearance <10 ml/min should be treated under expert supervision.
As a precaution, renal function should be monitored if renal functionis already impaired.

There may be some variation on the results of biochemical tests of renal function, but these do not appear to be of clinical importance.

Special care should be taken in patients with hepatic dysfunction.

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore the use in this patient group is not recommended.

Cefuroxime solutions are incompatible with aminoglycoside antibiotics (see section 6.2).

Emesis and diarrhoea due to treatment with cefuroxime (see section 4.8) might affect the efficacy of medicinal products which are simultaneously used, e.g. oral contraceptives. In case of emesis and diarrhoea oral contraceptives should, be supplemented with non-hormonal contraceptive measures.

Cefuroxime sodium use may result in a false positive Coombs test. This may interfere with the performance of cross matching tests with blood (see section 4.8).

Either the glucose oxidase or the hexokinase methods are recommended to determine the blood and plasma glucose levels in patients receiving Cefuroxime sodium. Cefuroxime does not interfere in the alkaline picrate assay for creatinine (see section 4.5).

Urine sugar tests using reduction methods may show false positive reactions; therefore enzymatic methods should be used.

This medicine product contains 3.6 mmol (or 78 mg) of sodium per 1500 mg dose which should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Potential nephrotoxic medicinal products and loop diuretics
Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide, aminoglycosides and amphotericin as concomitant use increases the risk of nephrotoxicity.

Bacteriostatic antibiotics
Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol concomitantly with cefuroxime. Synergism may exist with aminoglycosides and metronidazole.

Probenecid
Concomitant therapy with probenecid can reduce the renal excretion of cephalosporins accompanied by higher and prolonged concentrations of cefuroxime in serum (see section 5.2).

4.6 Pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of Cefuroxime for injection on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime reaches the embryo/fetus via the placenta. Due to the limited clinical experience, Cefuroxime Martindale Pharma® 750mg for Injection should only be used during pregnancy after careful risk/benefit assessment, especially during the first trimester.

Lactation
Cefuroxime is excreted in human milk. Cefuroxime should only be used during lactation after careful risk/benefit assessment. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

4.7 Effects on ability to drive and use machines

Cefuroxime may sometimes be associated with side effects, such as the very rarely occurring neurological undesirable effects (vertigo, restlessness, nervousness, confusion), that may impair the ability to drive a vehicle, to operate machinery or to work safely (see section 4.8).

4.8 Undesirable effects

Dependent on the dose and duration of the treatment approximately 3 % of all treated patients are expected to experience one or several of the adverse reactions mentioned below.

Frequency **Organ group**	***Very Common*** **(>1/100 and < 1/10)**	**Common (>1/1.000 and <1/100)**	**Rare (>1/10.000 and <1/1000)**	**Very rare (<1/10.000), including isolated reports**	**Not known**
Infections and infestations			Pseudomembranous colitis. As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. Candida, Enterococci and Clostridium difficile (see section 4.4).		
Blood and lymphatic system disorders		Thrombocytopenia, eosinophilic disorder, neutropenia and leukopenia	Decreased haemoglobin concentration, agranulocytosis	Haemolytic anaemia	
Immune system disorders			Serum sickness	Anaphylaxis See section 4.4	Angioedema
Nervous system disorders		Headache, dizziness		Vertigo, restlessness, Nervousness, confusion	
Gastrointestinal disorders	Gastrointestinal disturbances, diarrhoea, nausea				

	and vomiting				
Hepato-biliary disorders		Transient rise in serum liver enzymes ALT, AST and LDH and bilirubin		Jaundice	
Skin and subcutaneous tissue disorders	Skin rashes, urticaria, Pruritus,		Erythema multiforme Stevens-Johnson syndrome**,** Toxic epidermal necrolysis		
Renal and urinary disorders	Increased levels of creatinine and urea in serum, especially in patients with impaired renal function. See sections 4.2 & 4.4	Acute interstitial nephritis. Nephrotoxicity . Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment See sections 4.2 & 4.4			
General disorders and administration site conditions	Thrombophlebitis and pain following i.v. injection. After rapid i.v. administration heat sensations or nausea may occur.		Drug fever		
Investigations					The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood.

4.9 Overdose

Acute symptoms and signs of an overdose is cerebral irritation, which may lead to convulsions. There can be sequelae in form of brain damage.
The level of cefuroxime in serum can be reduced by increasing the diuresis or by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification
Pharmacotherapeutic group: Second-generation cephalosporins
ATC code: J01DC02

Mode of action

All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug to cell receptors, called Penicillin-Binding Proteins. After a β-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. Bacterial lysis is the end result.

PD/PK relationship

The efficacy is mainly determined by the length of time, during which the drug level is above the minimal inhibitory concentration of the pathogen.

Mechanism of resistance

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably derepressed in certain aerobic gram-negative bacterial species
- reduced affinity of penicillin-binding proteins for cefuroxime
- outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in gram-negative organisms
- drug efflux pumps

Methicillin-resistant staphylococci (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime.
Penicillin-resistant Streptococcus pneumoniae are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins.
Beta-lactamase negative, ampicillin resistant (BLNAR) strains of H. influenzae should be considered resistant to cefuroxime despite apparent in vitro susceptibility.
Strains of Enterobacteriaceae, in particular Klebsiella spp. and Escherichia coli that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

Breakpoints:

The clinical minimum inhibitory concentration (MIC) breakpoints (EUCAST, May 2009) are as follows

	Sensitive	Resistant
Enterobacteriaceae	≤ 8	> 8
S. pneumoniae	≤ 0.5	> 1
Streptococci other than *S. pneumoniae and* streptococcus groups A, B, C and G	≤ 0.5	> 0.5
H. influenzae	≤ 1	> 2
M. catarrhalis	≤ 1	> 2

Susceptibility of staphylococci to cefuroxime is inferred from the methicillin susceptibility.
The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.
Non-species related breakpoints: insufficient data

Susceptibility:

The prevalence of resistance may vary geographically and with time for selected species and local information 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. This has to be considered when interpreting the list below.

Commonly susceptible species
Gram positive aerobes
Staphylococcus aureus (methicillin-susceptible)
Streptococcus agalactiae
Streptococcus pyogenes
Gram negative aerobes
Proteus mirabilis
Species for which acquired resistance may be a problem
Gram positive aerobes
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae[1]
Gram negative aerobes
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Inherently resistant organisms
Gram positive aerobes
Enterococcus spp.
Listeria monocytogenes
Staphylococcus aureus (methicillin-resistant)[2]
Staphylococcus epidermidis (methicillin-resistant)
Gram negative aerobes
Acinetobacter baumannii
Burkholderia cepacia
Campylobacter spp.
Morganella morganii
Proteus vulgaris
Pseudomonas aeruginosa
Serratia spp.
Stenotrophomonas maltophilia
Anaerobes
Bacteroides spp.
Clostridium difficile
Others
Chlamydia spp.
Chlamydophila spp.
Legionella spp.
Mycobacterium spp.

Mycoplasma spp.

1. Streptococci resistant to penicillin are always resistant to cefuroxime
2. Staphylococci resistant to methicillin are resistant to other beta-lactams

5.2 Pharmacokinetic properties

Absorption
Cefuroxime is poorly absorbed from the gastro-intestinal tract and is given by intramuscular or intravenous injection or infusion as the sodium salt. Following intravenous doses of 750 mg and 1,500 mg, serum peak concentrations (C_{max}) were approximately 50 µg/ml and 100 µg/ml, respectively, after 15 minutes (t_{max}).

Peak plasma concentrations of 27 µg per ml have been achieved about 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose.

Distribution
Cefuroxime is widely distributed in the body and levels, that exceed the MIC-values of most pathogens, are achieved pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. The volume of distribution ranges between 9.3 and 15.8 l/1.73 m^2 in healthy adults. About 33% to 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Biotransformation
Cefuroxime is metabolized only to a minor extent (<5%).

Elimination
The elimination half-life ranges between about 70 and 80 min after intramuscular or intravenous administration in healthy adults. Most of the dose of cefuroxime is excreted unchanged in active form. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 6 hours; high concentrations are achieved in the urine. Small amounts of cefuroxime are excreted in bile. The renal clearance is 136.0 and 169.6 ml/min/1.73 m^2 after 0.5 and 1 g cefuroxime intravenous and 137.9 and 146.3 ml/min/1.73 m^2 after 0.750 and 1 g cefuroxime intramuscular, respectively. The elimination is impaired in patients with impaired renal function.
Concomitant administration of oral probenecid slows tubular secretion of cefuroxime and decreases renal clearance by approximately 40%.
Oral probenecid (1 g) prolonged the half-life by 63% and increased the area under the concentration-time curve of intravenous cefuroxime (750 mg) by up to 50%.

Cefuroxime is dialysable and small amounts are removed by peritoneal dialysis.

Linearity/non-linearity
The peak plasma concentration and the area under the concentration curve increase with increasing dose.

Pharmacokinetics in special patient groups
The half-life of cefuroxime is prolonged in patients with renal impairment associated with the risk of accumulation. The serum half-life is 4.2 hours at a creatinine clearance of 23 ml/min and 22.3 hours at a creatinine clearance of 5 ml/min. Therefore dose adjustment is required in patients with impaired renal function (see section 4.2).

The serum half-life is prolonged in preterm and term newborn infants during the first weeks of life (3 to 5 times the value in adults).

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide.

The most prominent treatment-related effect was tissue damage at the injection sites.

Investigations in rabbits and mice did not demonstrate reproductive toxicity or teratogenic-effects. Cefuroxime has been shown to pass the placenta.

Gamma-glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however, the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products and other solutions for injection except those mentioned in section 6.6.

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

Mixing of cefuroxime with sodium bicarbonate solutions significantly affects the colour of the solution. Therefore, this solution is not recommended for the dilution of cefuroxime. If required, the cefuroxime solution in water for injections can be introduced into the tubing of the giving set in patients receiving sodium bicarbonate solution by infusion.

6.3 Shelf Life

1 year
From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are responsibility of the user.

6.4 Special precautions for storage

Unopened: Store below 25ºC in the original carton in order to protect from light.
For storage conditions after reconstitution, see section 6.3

6.5 Nature and contents of container

Packed singly with 20 ml clear glass vial (Type - III) stoppered with bromo-butyl rubber plug, and sealed with Red Coloured flip-off aluminum seals.

6.6 Special precautions for disposal and other handling

Intravenous injection
Add water for injection immediately before use:
Dissolve the contents of the vial in 15 ml of water for injections
Shake until a clear solution is obtained.

The reconstituted solution is yellowish to brownish.

Differences in colour and intensity do not have any influence on the safety and efficacy. Following reconstitution the total volume of vial is 16 ml.

An aqueous solution of cefuroxime has a pH value of 6.0-8.5.

Cefuroxime can be mixed with the following solutions for injection:

- Water for injection
- sodium chloride 9 mg/ml (0,9%)solution
- glucose 50 mg/ml (5%) solution

As for all parenteral medicinal products, inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and practically free from particles.

For single use only. Any remaining solution should be discarded.

Empty vials and any unused medical products should be returned to pharmacy/supplier or to the local waste disposal site.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 361/30/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th June 2010

10 DATE OF REVISION OF THE TEXT