Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 300 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 300 mg clindamycin.

Excipient(s) with known effect:
Each capsule contains lactose monohydrate 228.57mg (approximately).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Powder blue capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapeutic indications
Clindamycin is indicated for the treatment of patients with serious infections caused by susceptible micro-organisms, particularly in recurrent infections, and not responding to first line antibiotics, and as an alternative treatment in the case of penicillin-allergic patients with infections caused by Gram-positive aerobic bacteria. It is also indicated in serious infections caused by susceptible anaerobic pathogens (see section 5.1).

- Pneumonia.
- Chronic sinusitis due to anaerobic bacteria.
- Tonsillitis.
- Skin and soft tissue infections.
- Bone and joint infections e.g. osteomyelitis and septic arthritis.
- Female pelvic and genital infections such as endometritis, pelvic cellulitis, paravaginal infections, tubo ovarian abscesses and salpingitis. Should be treated in combination with an antibiotic effective against Gram-negative aerobic bacteria.
- Intra-abdominal infections including peritonitis and abdominal abscess. Should be treated in combination with an antibiotic effective against Gram-negative aerobic bacteria.

As for all antibiotic, in vitro sensitivity tests must be performed in serious infections.

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

4.2 Posology and method of administration

Posology

Adults, adolescents over 12 years of age and the elderly:
The usual dose is 150 – 450 mg every six hours depending on the severity of the infection. For dosing below 300 mg other presentations of clindamycin are available.

Dosage in elderly
The dosage of clindamycin may require reduction in patients with sever renal or hepatic impairment due to prolongation of the serum half-life of this drug (see section 5.2). This is particularly important with parenteral dosage.

Paediatric population (over 1 month of age):
Clindamycin should be dosed based on total body weight regardless of obesity. The total daily dose should not exceed the maximum recommended daily dose for adults.
The usual daily dosage is 12 - 24 mg/kg in 4 divided doses.
Clindamycin Capsules are not suitable for children who are unable to swallow them whole. The use of whole capsules may not be suitable to provide the exact mg/kg doses required for the treatment of children.

Dosage in renal impairment
Clindamycin dosage modification is not necessary in patients with renal insufficiency.

The dose and method of administration is determined by the severity and sensitivity of the causative organism(s) and the condition of the patient. As for all antibiotics, in severe infections, in vitro sensitivity tests should be conducted. Alternative formulations of clindamycin are available for treating children for whom the capsules are unsuitable or for doses that cannot be reached by this pharmaceutical form. In case of severe clinical status parenteral therapy is preferred to oral therapy.

Note: In cases of beta-haemolytic streptococcal infections, treatment with Clindamycin Capsules should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

The duration of treatment depends on the clinical response of the patient. However, due to the risk of severe disruption of the faecal flora and its consequences (see sections 4.4), treatment should be kept to the minimum. If prolonged therapy is considered to be unavoidable, the patient should be carefully monitored for adverse effects (see section 4.4).

Method of administration
To be taken orally. Oral capsules should not be divided and should be swallowed with a glass of water and in an upright position.

The extent of absorption of Clindamycin Capsules is not appreciably modified by the presence of food.

4.3 Contraindications

Hypersensitivity to clindamycin, lincomycin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Severe hypersensitivity reactions, including severe skin reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) have been reported in patients receiving clindamycin therapy. If a hypersensitivity or severe skin reaction occurs, clindamycin should be discontinued and appropriate therapy should be initiated (see sections 4.3 and 4.8).

Use in patients with atopic syndrome
Care should be observed in the use of <Invented name> in atopic individuals, e.g. asthma and allergy.

Clostridium Difficile associated diarrhoea
Clindamycin should only be used in the treatment of serious infections and when the possible benefit of using clindamycin is considered to outweigh the risk of antibiotic-associated diarrhoea or colitis, which may progress to pseudomembraneous colitis, peritonitis, shock, toxic megacolon and death.

Studies indicate a toxin(s) produced by clostridia (especially *Clostridium difficile*) is the principal cause of antibiotic-associated colitis. These studies also indicate that this toxigenic clostridium is usually sensitive *in vitro* to vancomycin. When 125-500 mg of vancomycin is administered orally four times a day, there is a rapid observed disappearance of the toxin from faecal samples and a coincident recovery from the diarrhoea.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. This has been reported with use of nearly all antibacterial agents, including clindamycin. *Clostridium difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhoea (CDAD) and is a primary cause of "antibiotic-associated colitis".

It is important to consider the diagnosis of CDAD in patients who present with diarrhea subsequent to the administration of antibacterial agents. This may progress to colitis, including pseudomembranous colitis (see Section 4.8), which may range from mild to fatal colitis. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including clindamycin, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

Pseudomembranous colitis can develop during, or two or three weeks following the administration of clindamycin. These intestinal complications are more likely to be severe and to become life-threatening in older patients or patients who are debilitated. Diagnosis is usually made by the recognition of the clinical symptoms, but can be substantiated by endoscopic demonstration of pseudomembraneous colitis. Stool culture for Clostridium difficile and/or assay for Clostridium difficile toxin may be helpful to diagnosis.

Caution should also be used when prescribing clindamycin for individuals with a history of gastro-intestinal disease, especially colitis. If diarrhoea or colitis occurs during therapy, clindamycin should be discontinued immediately and appropriate diagnostic and therapeutic measures should be instituted. It should be noted that the onset of these intestinal complications of clindamycin treatment may be delayed until several weeks following the cessation of therapy. The most commonly implicated cause is an overgrowth of toxin-producing Clostridium difficile as a result of disruption of the bowel flora by clindamycin.

Clindamycin Capsules should not be used in patients with diarrhoea or intestinal inflammatory disease.

Liver and Kidney function tests during prolonged therapy
If therapy is prolonged liver and kidney function tests and blood counts should be performed. Such monitoring is also recommended in neonates and infants. Safety and appropriate dosage in infants less than one month old have not been established.
Acute kidney injury, including acute renal failure, has been reported infrequently. In patients suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs, monitoring of renal function should be considered (see section 4.8).
Hepatic and renal insufficiency: In severe renal impairment, peak plasma levels of clindamycin may be up to three times normal and the elimination half-life is prolonged. Dose reduction and/or an increased dose interval should be considered. In moderate and severe degrees of hepatic impairment, peak plasma levels of clindamycin are higher than normal and the elimination half-life is prolonged. Dose reduction and/or an increased dose interval should be considered.
Serum clindamycin levels should be estimated. Periodic liver, kidney function and haematological tests should be carried out during prolonged therapy.

Non-susceptible organisms
The use of clindamycin may result in overgrowth of non-susceptible organisms, particularly yeasts. Prolonged administration of an anti-infective may result in super-infection due to organisms resistant to the anti-infective.

Diffusion into cerebrospinal fluid
Clindamycin does not cross the blood-brain barrier. Therefore, clindamycin should not be used in complications including meningeal infections.

Cross Resistance
Attention should also be paid to the possibility of cross resistance to macrolides and lincosamides for some individual bacterial strains (see section 5.1).

Clindamycin should not be given in patients with acute viral infections of the respiratory tract. Clindamycin should be reserved for serious infections, where less toxic antibiotics are considered inappropriate.

Excipients:
This medicinal product contains lactose:
Lactose intolerance: Clindamycin capsules contain lactose; patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Clindamycin administered by injection has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin and its chemically-related macrolides *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

Clindamycin Capsules should not be prescribed concurrently with erythromycin.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.

Co-administration of clindamycin with inhibitors of CYP3A4 and CYP3A5
Clindamycin is metabolized predominantly by CYP3A4, and to a lesser extent by CYP3A5, to the major metabolite clindamycin sulfoxide and minor metabolite N-desmethylclindamycin. Therefore, inhibitors of CYP3A4 and CYP3A5 may reduce clindamycin clearance and inducers of these isoenzymes may increase clindamycin clearance. In the presence of strong CYP3A4 inducers such as rifampicin, monitor for loss of effectiveness.

In vitro studies indicate that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6 and only moderately inhibits CYP3A4. Therefore, clinically important interactions between clindamycin and co-administered drugs metabolized by these CYP enzymes are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy
Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal blood concentrations.

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

Clindamycin should be used in pregnancy only if clearly needed.

Breast-feeding
Clindamycin is excreted in human milk after systemic use (see section 5.2) and can have unintended effects on the microbiota of breastfed infants of exposed mothers related to the exposure in the GI track.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from clindamycin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability.

4.7 Effects on ability to drive and use machines

Clindamycin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Gastrointestinal adverse effects are experienced by approximately 8% of the patients, mainly as diarrhoea.

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency.

The frequency grouping is defined using 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) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	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 available data)
Infections and infestations		pseudomembranous colitis*#				*clostridium difficile* colitis*, Vaginal infection*
Blood and lymphatic system disorders						Agranulocytosis* Neutropenia*, Thrombocytopenia*, leucopenia*, eosinophilia.
Immune system disorders						Anaphylactic shock*, anaphylactoid reactions*,anaphylactic reaction*, hypersensitivity*
Nervous system disorders						Dysgeusia
Gastrointestinal disorders		Diarrhoea, Abdominal pain	Vomiting, Nausea			Oesophageal ulcer*‡ oesophagitis*‡
Hepato-biliary disorders						Jaundice*
Skin and subcutaneous tissue disorders			Rash maculopapular, Urticaria			Toxic epidermal necrolysis (TEN)*, Stevens-Johnson syndrome (SJS)*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalized Exanthematous pustulosis (AGEP)*, angioedema*, dermatitis exfoliative*, dermatitis bullous*, erythema multiforme*, pruritus, rash morbilliform,
Renal and urinary disorders						Acute kidney injury#
Investigations		Liver function test abnormal				

* ADR identified post-marketing.

‡ ADRs apply only to oral formulations.
# See section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms from overdosing are nausea, vomiting and diarrhoea.

In cases of overdosage that may have led to adverse reactions, therapy should be discontinued and the usual emergency treatment, including corticosteroids, adrenaline and antihistamines, instituted.

The serum biological half-life of clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics for systemic use, Lincosamides,
ATC code: J01FF01.

Mechanism of action:
Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as Clindamycin bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit the early stages of protein synthesis. Clindamycin has predominantly bacteriostatic action although high concentrations may be slowly bactericidal against sensitive strains.

Mechanisms of resistance:
Resistance to clindamycin can be due to the following mechanisms:
Resistance to staphylococci and streptococci is often based on methyl groups increasingly binding to the 23S rRNA (so-called constitutive MLS_B-resistance), whereby the binding affinity of clindamycin to the ribosome is highly reduced.
Less frequently encountered resistance mechanisms involve modification of the antibiotic and active efflux.
The majority of methicillin-resistant S. aureus (MRSA) shows the constitutive MLSB type of resistance and is therefore resistant to clindamycin. Infections caused by macrolide-resistant staphylococci should not be treated with clindamycin, also when in-vitro susceptibility was proven, because therapy may lead to selection of mutants with constitutive MLSB resistance.
Strains with constitutive MLSB resistance show complete cross-resistance of clindamycin with lincomycin, macrolides (e.g. azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin) as well as streptogramin B.
There is cross-resistance of pathogens towards clindamycin and lincomycin.
Susceptibility testing breakpoints:

- The prevalence of acquired 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. Particularly in severe infections or therapy failure microbiological diagnosis with verification of the pathogen and its susceptibility to clindamycin is recommended.
- Resistance is usually defined by susceptibility interpretive criteria (breakpoints) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for systemically administered antibiotics.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are presented below.

Table 1. EUCAST Susceptibility Interpretive Criteria for Clindamycin (2022-01-01, v12.0)

Organisms	**Minimum Inhibitory Concentration (MIC) breakpoints (mg/L)**	
	Susceptible (S ≤)	**Resistant (R >)**
Bacillus spp. except B. anthracis	1	1
Bacteroides spp.	4	4
Clostridium perfringens	0.25	0.25
Corynebacterium spp.	0.5	0.5
Cutibacterium acnes	0.25	0.25
Fusobacterium necrophorum	0.25	0.25
Prevotella spp.	0.25	0.25
Staphylococcus spp.	0.25	0.25
Streptococcus groups A, B, C and G	0.5	0.5
Streptococcus pneumoniae	0.5	0.5
Viridans group streptococci	0.5	0.5

Latest susceptibility testing interpretive criteria endorsed by the CHMP/CMDh are listed on the EMA website; available on the following URL: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

PK/PD relationship:
The efficacy is related to the area under the concentration–time curve of the unbound fraction of the agent that exceeds the minimum inhibitory concentration (MIC) of the pathogen (*f*AUC/MIC).

Antimicrobial activity:
Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

Aerobicbacteria
Gram-positive bacteria:

- *Staphylococcus aureus* (methicillin-susceptible isolates)
- *Coagulase-negative staphylococci (*methicillin-susceptible isolates)
- *Streptococcus pneumoniae* (penicillin-susceptible isolates)
- Beta-hemolytic streptococci groups A, B, C, and G
- Viridans group *streptococci*
- *Corynebacterium* spp.

Gram-negative bacteria

- *Chlamydia trachomatis*

Anaerobic bacteria
Gram-positive bacteria

- *Actinomyces species.*
- *Clostridium spp. (except Clostridium difficile)*
- *Eggerthella (Eubacterium)* spp.
- *Peptococcus species;*
- *Peptostreptococcus species;(Finegoldia magna, Micromonas micros)*
- *Propionibacterium acnes*

Gram-negative bacteria

- *Bacteroides* spp.
- *Fusobacterium* spp.
- *Gardnerella vaginalis*
- *Prevotella* spp.

Species for which acquired resistance may be a problem

Aerobic bacteria

Gram-positive bacteria

- *Staphylococcus aureus (methicillin-susceptible isolates)*
- *Coagulase-negative staphylococci (except methicillin-resistant isolates)*
- *Streptococcus pneumoniae (except penicillin-resistant isolates)*

Gram-negative bacteria

- *Moraxella catarrhalis*

Anaerobic bacteria
Gram-negative bacteria

- *Bacteroides fragilis*

Inherently resistant organisms
Aerobic bacteria
Gram-positive bacteria

- *Coagulase-negative staphylococci (methicillin-resistant isolates)*
- *Enterococcus faecalis*
- *Enterococcus faecium*

Gram-negative bacteria

- *Haemophilus influenzae*

Anaerobic bacteria

Gram-positive bacteria

- *Clostridium difficile*

5.2 Pharmacokinetic properties

Absorption
Serum level studies with a 150mg oral dose of Clindamycin in 24 normal adult volunteers showed that Clindamycin was rapidly absorbed after oral administration. An average peak serum level of 2.5 mcg/mL was reached in 45 minutes: serum levels averaged 1.51 mcg/mL at 3 hours and 0.70 mcg/mL at 6 hours. Absorption of an oral dose is virtually complete (90%) and the concomitant administration of food dose not appreciably modify the serum concentrations; serum levels have been uniform and predictable from person to person and dose to dose. Serum levels studies following multiple dose of Clindamycin for up to 14 days show no evidence of accumulation or altered metabolism of drug. Serum half-life of Clindamycin is increased slightly in patients with markedly reduced renal function. Haemodialysis and peritoneal dialysis are not effective in removing Clindamycin from the serum. Concentrations of Clindamycin in the serum increased linearly with increased dose. Serum levels exceed the MIC (minimum inhibitory concentrations) for most indicated organisms for at least six hours following administration of the usually recommended doses.

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastro-intestinal tract. Plasma concentrations of 2 to 3 mg/L occur within one hour after a 150 mg dose of clindamycin. Absorption is not significantly diminished by food in the stomach, but the rate of absorption may be reduced.

Distribution
Clindamycin is widely distributed in body fluids and tissues including bones. But it does not reach the cerebrospinal fluid in significant concentrations. It diffuses across the placenta into the foetal circulation and appears in breast milk. Concentrations

in human breast milk have been reported to be up to 3.8 µg/mL shortly after a 600 mg IV dose, falling to about 1 µg/mL at about 2 h. The Cmax after oral dosing is not known but milk levels up to 1.2 µg/mL have been reported after a 150 mg oral dose. High concentrations occur in bile.
It accumulates in leucocytes and macrophages. About 40 - 90% of clindamycin in the circulation is bound to plasma proteins. The mean volume of distribution is 1.1 L/kg.

Biotransformation
In vitro studies in human liver and intestinal microsomes indicated that clindamycin is predominantly oxidized by CYP3A4, with minor contribution from CYP3A5, to form clindamycin sulfoxide and a minor metabolite, N-desmethylclindamycin. The average biological half-life is 2.4 hours.
Clindamycin undergoes metabolism, presumably in the liver, to the active N-demethyl and sulphoxide metabolites and also some inactive metabolites. The plasma elimination half-life is 2 – 3 hours, although this may be prolonged in neonates, especially when premature, and in patients with moderate or severe degrees of renal or hepatic impairment. About 10% of the drug is excreted in the urine as active drug or metabolite and about 4% in the faeces; the remainder is excreted as inactive metabolites. Clindamycin is not effectively removed from the blood by haemodialysis or peritoneal dialysis.

Elimination
Approximately 10% of the bioactivity is excreted in the urine and 3.6% in the faeces; the remainder is excreted as bioinactive metabolites. Doses of up to 2 grams of Clindamycin per day for 14 days have been well tolerated by healthy volunteers, except that the incidence of gastrointestinal side effects is greater with the higher doses. No significant levels of Clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunteers (61-79 years) and younger adults (18-39 years) indicate that age alone does not alter Clindamycin pharmakinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentrations time curve) after IV administration of Clindamycin phosphate. After oral administration of Clindamycin, elimination half-life is increased to approximately 4.0hours (range 3.4-5.1 h) in the elderly compared to 3.2 hours (range 2.1-4.2 h) in younger adults. The extent of absorption however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function.

Characteristics in patients
Elderly:
The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin are not altered by increased age.

In patients with reduced renal function:
In the presence of kidney diseases, elimination half-life is prolonged; however, a dosage reduction is unnecessary in the event of mild to moderate impairment of renal function.

In patients with reduced liver function:
In patients with moderate to severe reduced liver function the half-life is prolonged, but when giving the dose every 8 hour accumulation is rarely seen. Dose reduction is normally not necessary in patients with reduced liver function.

Obese paediatric patients aged 2 to 18 years and obese young adults aged 18 to 20 years:
An analysis of pharmacokinetic data in paediatric patients (2 to 18 years) and young adults (18 to 20 years) demonstrated that the clearance and volume of distribution of clindamycin, when normalized to total body weight, are comparable between obese and non-obese patients.

5.3 Preclinical safety data

There is no evidence of teratogenic effect in animals, nor to date in man.

Carcinogenesis:
Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential.

Mutagenesis:
Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Reproductive toxicity:
Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

In oral embryo foetal development studies in rats and subcutaneous embryo foetal development studies in rats and rabbits, no developmental toxicity was observed except at doses that produced maternal toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents
Lactose monohydrate
Maize Starch
Magnesium stearate
Talc

Capsule Body & Cap
Gelatin
Titanium dioxide (E171)
Patent blue V (E131)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister packs composed of PVC / PE / PVdC aluminium foil; pack sizes: 4, 8, 16, 20, 24, 30, 32, 40 and 100.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product does not require any special storage conditions.

7 MARKETING AUTHORISATION HOLDER

EG (Eurogenerics)
Bus B22
Esplanade S N
Brussels
Brussels-Capital Region
1020
Belgium

8 MARKETING AUTHORISATION NUMBER

PA25213/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th May 2009

Common renewal date: 15th February 2014

10 DATE OF REVISION OF THE TEXT

September 2023