SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
   Cefotaxime 2g Powder for Solution for Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Cefotaxime Sodium for Injection BP 2g contains 2097mg Cefotaxime Sodium
   (equivalent to 2000mg Cefotaxime) per vial.

   Each gram of Cefotaxime Sodium for Injection contains approximately 48mg
   (2.09mmol) of sodium.

3. PHARMACEUTICAL FORM
   Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
   Cefotaxime is used for the treatment of infections due to Gram-negative bacteria
   which are sensitive or resistant to first or second generation cephalosporins.
   Cefotaxime is also active against a number of Gram-positive bacteria.

   Cefotaxime is therefore indicated for the treatment of the following conditions when
   caused by bacteria of known sensitivity or before the infecting organism has been
   identified.

   Septicaemias
   Respiratory tract infections: bacterial pneumonia, acute and chronic bronchitis,
   infected bronchiectasis, lung abscess, post-operative chest infections.
   Urinary tract infections: acute and chronic pyelonephritis, cystitis and asymptomatic
   bacteriuria.
   Soft tissue infections: peritonitis, cellulitis, wound infections.
   Bone and joint infections: osteomyelitis, septic arthritis.
   Obstetric and gynaecological infections: pelvic inflammatory disease.
   Gonorrhoea including that unsuccessfully treated with penicillin.
   Meningitis

   Other sensitive infections which may be suitably treated with a parenteral antibiotic

   Cefotaxime may also be used prophylactically to reduce the incidence of certain post-
   operative infections in patients undergoing surgical procedures that are classified as
   contaminated or potentially contaminated, or in clean operations where infection
   would have serious effects. To ensure that adequate local tissue concentrations are
   achieved at the time of contamination, Cefotaxime should be administered
   immediately before surgery and continued in the immediate post-operative period as
   necessary. Administration should usually be stopped within 24 hours as
   continuing use of any antibiotic in the majority of surgical procedures does not reduce
   the incidence of subsequent infection.
4.2 **Posology and method of administration**

*Route of administration:*

Cefotaxime may be administered by intramuscular or intravenous injection, or by intravenous infusion over 20-60 minutes. The severity of the infection, sensitivity of the infecting organisms and the status of the patient should be assessed in order to determine the route of administration, dose and dose frequency of Cefotaxime. Treatment with Cefotaxime may be started before the results of sensitivity tests are known.

*Intravenous administration (injection or infusion):*

For intermittent I.V. injections, the solution must be injected over a period of 3 to 5 minutes. During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter.

Cefotaxime and aminoglycosides should not be mixed in the same syringe or perfusion fluid.

**Dosage**

*Adults:* The recommended dosage for mild to moderate infections is 1g 12 hourly. However, dosage may be varied according to the severity of the infection, sensitivity of causative organisms and condition of the patient.

In severe infections dosage may be increased up to 12g daily given in 3 or 4 divided doses. For infections caused by sensitive Pseudomonas spp. daily doses of greater than 6g will usually be required.

*Children:* 100-150 mg/kg/day in 2 to 4 divided doses is the usual dosage range for children. Up to 200 mg/kg/day, in divided doses, may be required in cases of severe infection.

*Neonates:* 50 mg/kg/day in 2 to 4 divided doses is the recommended dosage. Doses of 150-200 mg/kg/day, in divided doses, have been given in cases of severe infection.

*Elderly:* Specific dosage adjustments are not required for the elderly.

*Renal impairment:* In patients with severe renal failure (GFR < 5ml/min = serum creatinine of approximately 750 micromol/l) it is necessary to reduce the dosage of Cefotaxime. An initial loading dose of 1g should be administered. Thereafter, the daily dose should be halved without change in the frequency of dosing, e.g. 1g 12 hourly becomes 0.5g 12 hourly, 1g 8 hourly becomes 0.5g 8 hourly and so on. The dosage may require further modification depending on the course and severity of the infection and the general physical status of the patient.

*Gonorrhoea:* A single intramuscular or intravenous injection of 1g may be given

4.3 **Contraindications**

- Known or suspected hypersensitivity to cephalosporins
- In patients with a history of hypersensitivity to Cefotaxime and/or to any component of Cefotaxime 1g Powder for Solution for Injection/Infusion

Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4)

For pharmaceutical forms containing lidocaine:
- known history of hypersensitivity to lidocaine or other local anesthetics of the amide type
- non-paced heart block
- severe heart failure
- administration by the intravenous route
- infants aged less than 30 months of age

4.4 Special warnings and precautions for use

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms, such as Enterococcus spp. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures, like specific anti-microbial therapy, should be taken where clinically necessary.

- Anaphylactic reactions

Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 and 4.8).

If a hypersensitivity reaction occurs, treatment must be stopped.

The use of cefotaxime is strictly contra-indicated in subjects with a previous history of immediate type hypersensitivity to cephalosporins.

Preliminary enquiry about hypersensitivity to penicillin and other β Lactam antibiotics is necessary before prescribing cephalosporins since cross allergy is reported in 5-10% of cases.

Since cross allergy exists between penicillins and cephalosporins, use of the latter should be undertaken with extreme caution in penicillin sensitive subjects.

Combination with lidocaine for intramuscular injection must not used in subjects with a previous history of hypersensitivity to this product.

- Serious bullous reactions
Cases of serious bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with cefotaxime (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

- Clostridium difficile associated disease (e.g. pseudomembranous colitis)
Cefotaxime may predispose patients to pseudomembranous colitis. This side effect, which may occur more frequently in patients receiving higher doses for prolonged periods, should be considered as potentially serious.

Diarrhea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of *Clostridium difficile* associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudo-membranous colitis.

The diagnosis of this rare but possibly fatal condition can be confirmed by endoscopy and/or histology.

It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of cefotaxime.

If a diagnosis of pseudomembranous colitis is suspected by toxin detection, cefotaxime should be stopped immediately and appropriate specific antibiotic therapy (e.g. vancomycin or metronidazole) should be started without delay.

*Clostridium difficile* associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given.

- **Haematological reactions**
  Leukopenia, neutropenia and, more rarely, agranulocytosis may develop during treatment with cefotaxime, particularly if given over long periods. For treatment courses lasting longer than 7-10 days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia.

  Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anemia have also been reported. (see section 4.8)

- **Patients with renal insufficiency**
  The dosage should be modified according to the creatinine clearance calculated, refer to Section 4.2 Renal impairment.

  Caution should be exercised if cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs (see section 4.5). Renal function must be monitored in these patients, the elderly, and those with pre-existing renal impairment.

- **Neurotoxicity**
  High doses of beta-lactam antibiotics, including cefotaxime, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

- **Precautions for administration**
During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed (see section 4.2). See section 4.3 for contraindications for formulations containing lidocaine.

Cefotaxime Sodium must never be constituted with lidocaine for intravenous use, or for use in infants under 30 months, or patients with unpaced heart block or severe heart failure.

- Effects on Laboratory Tests
  As with other cephalosporins a positive Coombs' test has been found in patients treated with cefotaxime. This phenomenon can interfere with the cross-matching of blood.

Urinary glucose testing with non-specific reducing agents may yield false-positive results. This phenomenon is not seen when a glucose-oxydase specific method is used.

- Sodium intake
  The sodium content of cefotaxime sodium (48.2 mg/g) should be taken into account when prescribing to patients requiring sodium restriction.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of high-dose cephalosporin antibiotics with aminoglycoside antibiotics or potent diuretics such as furosemide should be avoided as these combinations are suspected to adversely affect renal function. As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide). Renal function must be monitored (see section 4.4).

However, if used according to the recommended dosage, Cefotaxime is unlikely to adversely affect renal function.

Probenecid interferes with the renal tubular transfer of cephalosporins, thereby delaying their excretion and increasing their plasma concentrations.

4.6 Pregnancy and lactation

Pregnancy

The safety of cefotaxime has not been established in human pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are, however, no adequate and well controlled studies in pregnant women.

Cefotaxime crosses the placental barrier. Therefore, cefotaxime should not be used during pregnancy especially during the first trimester unless the anticipated benefit outweighs any potential risks.
**Lactation**
Cefotaxime passes into human breast milk.

Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonisation by yeast-like fungi, and sensitisation of the infant cannot be excluded.

Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

**4.7 Effects on ability to drive and use machines**
There is no evidence that cefotaxime directly impairs the ability to drive or to operate machines. High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

**4.8 Undesirable effects**
Mild and transient adverse reactions to Cefotaxime have been reported, albeit infrequently.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
<th>Not known (cannot be estimated from available data)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Superinfection (see section 4.4) Candidiasis</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td></td>
<td>Leukopenia Eosinophilia (reversible when treatment is ceased) Thrombocytopenia (on stopping of treatment) Rapidly reversible Eosinophilia</td>
<td>Granulocytopenia (4) Neutropenia (reversible when treatment is ceased) Agranulocytosis (4) (see section 4.4) Haemolytic Anaemia (for cases of treatment lasting longer than 10 days, blood count should therefore be monitored)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system</td>
<td></td>
<td></td>
<td>Jarisch-Herxheimer</td>
<td></td>
<td></td>
<td>Hypersensitivity reactions</td>
</tr>
</tbody>
</table>

*(Note: The table uses the terms Very Common, Common, Uncommon, Rare, Very rare, and Not known to categorize adverse effects. The numbers in parentheses indicate the frequency range.)*
<table>
<thead>
<tr>
<th>disorders</th>
<th>reaction</th>
<th>Anaphylactic reactions</th>
<th>Angioedema</th>
<th>Bronchospasm</th>
<th>Anaphylactic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Convulsions (see section 4.4)</td>
<td>Headache</td>
<td>Dizziness</td>
<td>Encephalopathy(^{(1)})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g. impairment of consciousness, abnormal movements, convulsions)</td>
<td>(see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Arrhythmia</td>
<td>following rapid bolus infusion through central venous catheter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea (sometimes a symptom of pseudomembranous colitis)</td>
<td>Nausea</td>
<td>Vomiting</td>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pseudomembranous colitis</td>
<td>(see section 4.4)</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin</td>
<td>Hepatitis(^{(2)})</td>
<td>(sometimes with jaundice)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous tissue disorders</td>
<td>Rash, Pruritus, Urticaria</td>
<td>Erythema multiforme</td>
<td>Stevens-Johnson syndrome</td>
<td>Toxic epidermal Necrolysis(^{(3)})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and Urinary disorders</td>
<td>Decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides)</td>
<td>Interstitial nephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and Formulations:</td>
<td>Fever, drug fever, Inflammatory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{(1)}\) Encephalopathy

\(^{(2)}\) Hepatitis

\(^{(3)}\) Toxic epidermal necrolysis
<table>
<thead>
<tr>
<th>administration site conditions</th>
<th>Pain at the injection site (more likely to occur with higher doses)</th>
<th>reactions at the injection site, including phlebitis (5)/thrombophlebitis</th>
<th>the solvent contains lidocaine: Systemic reactions to lidocaine</th>
</tr>
</thead>
</table>
| Musculoskeletal and connective disorders | Arthralgia | (1) Administration of high doses of cephalosporins, particular in patients with renal insufficiency, may result in encephalopathy.  
(2) Postmarketing experience  
(3) As with other cephalosporins, occasional cases of bullous reactions such as Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have also been reported.  
(4) As with other beta-lactam antibiotics, granulocytopenia and more rarely agranulocytosis may develop during treatment, particularly if given over long periods.  
(5) Occasionally, phlebitis has been reported in patients receiving intravenous Cefotaxime. However, this has rarely been a cause for discontinuation of treatment.

Jarisch-Herxheimer reaction

For the treatment of borreliosis (Lyme disease), a Jarisch-Herxheimer reaction may develop during the first days of treatment.  
The occurrence of one or more of the following symptoms has been reported after several week's treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of breathing, joint discomfort. To some extent these manifestations are consistent with the symptoms of the underlying disease, for which the patient is being treated.

Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been observed. These laboratory abnormalities may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

4.9 Overdose

Symptoms of overdose may largely correspond to the profile of side effects.

There is a risk of reversible encephalopathy in cases of administration of high doses of beta-lactam antibiotics including cefotaxime particularly in patients with renal impairment.

In case of overdose, cefotaxime must be discontinued, and supportive treatment initiated, which includes measures to accelerate elimination, and symptomatic treatment of adverse reactions (e.g. convulsions).
No specific antidote exists. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic classification: Cephalosporins and related substances
ATC code: JOIDAIO

Cefotaxime is a broad spectrum bactericidal cephalosporin antibiotic. Cefotaxime is exceptionally active in vitro against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram positive bacteria.

Bacteriology:
Cefotaxime-sensitive Gram-negative bacteria include:
- Escherichia coli
- Haemophilus influenzae including those resistant to ampicillin
- Klebsiella spp.
- Proteus spp. (indole positive and indole negative species)
- Enterobacter spp.
- Neisseria spp. (including B-lactamase producing strains of N. gonorrhoea)
- Salmonella spp. (including S typhi)
- Shigella spp.
- Providencia spp.
- Serratia spp.
- Citrobacter spp.

Cefotaxime has useful in vitro activity against Pseudomonas and Bacteroides species but some strains of Bacteroides fragilis are resistant. There is in vitro evidence of synergy between Cefotaxime and aminoglycoside antibiotics such as gentamicin against some species of Gram-negative bacteria including some strains of Pseudomonas. No in vitro antagonism is reported. In severe infections caused by Pseudomonas spp. the addition of an aminoglycoside antibiotic may be indicated.

Cefotaxime-sensitive Gram-positive bacteria include:
- Staphylococci (including coagulase-positive, coagulase-negative and penicillinase-producing strains).
- Beta-haemolytic and other streptococci such as Streptococcus mitis (viridans). Many strains of enterococci, e.g. Streptococcus faecalis, are relatively resistant.
- Streptococcus (Diplococcus) pneumonia.
- Clostridium spp.

5.2 Pharmacokinetic properties
After a 1000mg intravenous bolus, mean peak plasma concentrations of Cefotaxime usually range between 81 and 102µg/ml. Doses of 500mg and 2000mg produce plasma concentrations of approximately 38 and 200µg/ml, respectively. There is no accumulation following administration of 1000mg intravenously or 500mg intramuscularly for 10 or 14 days.
The apparent volume of distribution at steady-state of Cefotaxime is 21.6L/1.73m² after 1g intravenous 30 minute infusion. The reported degree of protein binding is approximately 40%.

Concentrations of Cefotaxime (usually determined by non-selective assay) have been studied in a wide range of human body tissues and fluids. Cerebrospinal fluid concentrations are low when the meninges are not inflamed, but are between 3 and 30 µg/ml in children with meningitis.

Cefotaxime usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4µg / ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of Cefotaxime and desacetylcefotaxime are attained in bile.

Cefotaxime is partially metabolised prior to excretion. The principal metabolite is the microbiologically active product, desacetylcefotaxime. Most of a dose of Cefotaxime is excreted in the urine about 60% as unchanged drug and a further 24% as desacetylcefotaxime. Plasma clearance is reported to be between 260 and 390ml/minute and renal clearance 145 to 217ml/minute.

After intravenous administration of Cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours.

In neonates the pharmacokinetics are influenced by gestational and chronological age, the half life being prolonged in premature and low birth weight neonates of the same age.

In severe renal dysfunction the elimination half-life of Cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetylcefotaxime is increased to about 10 hours. Total urinary recovery of Cefotaxime and its principal metabolite decreases with reduction in renal function.

5.3 Preclinical safety data

The following is a summary of the information available from published material. Cefotaxime Sodium has a very low order of toxicity. Following administration by the oral and intramuscular routes, no LD₅₀ values could be determined and even using intravenous administration the drug exhibited a low order of lethality.

Repeated dose toxicity studies in rats and dogs ranging from 30 days to 6 months in duration using a wide range of doses have been reported. Manifestations of toxicity included, local reactions at the injection site, enlargement of the caecum and some nephrotoxicity. However, many animals showed no effects at all and the drug was well tolerated. Nephrotoxic potential of Cefotaxime in rats following intramuscular injection has been studied. The study reported the threshold dose for renal tubular toxicity to be 5g/kg.
Reproductive toxicity studies in rats and mice showed no adverse effects on male or female fertility. No teratogenic effects were observed in rats or mice nor was there any evidence of mutagenicity using the Ames and micronucleus tests. Carcinogenicity studies have not been conducted.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
None.

6.2 **Incompatibilities**
Cefotaxime sodium should not be mixed with alkaline solutions such as sodium bicarbonate injection or solutions containing aminophylline.

6.3 **Shelf life**
*For the medicinal product as packaged for sale:*
24 months

*For the constituted solutions:*
Chemical and physical stability for 24h at 25°C has been demonstrated in the infusion fluids listed in section 6.6.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions before use are the responsibility of the user and would normally not be longer than 24h at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 **Special precautions for storage**
Do not store above 25°C.
Keep container in the outer carton in order to protect from light. Single use only.

6.5 **Nature and contents of container**
Cefotaxime is supplied in tubular glass vials with polymer-coated halobutyl rubber stoppers, each containing 2g Cefotaxime as Cefotaxime Sodium. The vials are boxed individually and in packs of 10, 25 or 50 vials. Not all pack sizes may be marketed.

6.6 **Instructions for use/handling**
*For intravenous and intramuscular injection:* Dissolve Cefotaxime Sodium for Injection BP in Water for Injection PhEur according to the table below. Shake well until dissolved. The entire contents, of the vial should be withdrawn into the syringe and used immediately.

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Volume of Water for Injection to be added</th>
</tr>
</thead>
<tbody>
<tr>
<td>2g</td>
<td>10ml</td>
</tr>
</tbody>
</table>

*For intravenous infusion:* Dissolve 1-2g Cefotaxime Sodium for Injection in 40-100ml of Water for Injection PhEur or in one of the infusion fluids listed below.

- Sodium Chloride Injection BP
• 5% Dextrose Injection BP
• Dextrose and Sodium Chloride Injection BP
• Compound Sodium Lactate Injection BP (Ringer-Lactate Injection)

Cefotaxime is compatible with metronidazole infusion (500mg/100ml), or 1% lidocaine but refer to section 4.4 'Special warnings and precautions for use'. These solutions should be used immediately.

Discard immediately if infusion solution is not clear and deposit free.

7. **MARKETING AUTHORISATION HOLDER**
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire
WA16 0PF
United Kingdom

8. **MARKETING AUTHORISATION NUMBER**
PL 35507/0003

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
16th February 2010

10. **DATE OF REVISION OF THE TEXT**
30th August 2011