New Zealand Data Sheet

1. PRODUCT NAME

| Ibiamox® 250mg Powder for injection |
| Ibiamox® 500mg Powder for injection |
| Ibiamox® 1000mg Powder for injection |

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The amoxicillin is present as the sodium salt in Ibiamox® (1059mg of amoxicillin sodium is equivalent to approximately 1000mg of amoxicillin).

| Ibiamox® 250mg Powder for injection contains 250mg amoxicillin. |
| Ibiamox® 500mg Powder for injection contains 500mg amoxicillin. |
| Ibiamox® 1000mg Powder for injection contains 1000mg amoxicillin. |

3. PHARMACEUTICAL FORM

Ibiamox® vials: white to cream powder packed in clear glass vials for reconstitution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Ibiamox® is indicated for the prophylaxis of endocarditis: to prevent bacteraemia associated with procedures in patients at risk of developing bacterial endocarditis.
- Ibiamox® is indicated in adults and children for the treatment of the following infections (see sections 4.2, 4.4 and 5.1):
  - Upper and lower respiratory tract infections
  - Genito-urinary tract infections
  - Skin and soft tissue infections

Ibiamox® is indicated for the treatment of infections due to susceptible strains of the following organisms:

<table>
<thead>
<tr>
<th>Gram-negative organisms</th>
<th>Gram-positive organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae</td>
<td>Streptococcus species</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>Non-penicillinase-producing-staphylococci</td>
</tr>
<tr>
<td>Neisseria gonorrhoea</td>
<td></td>
</tr>
</tbody>
</table>

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.
4.2. Dose and method of administration

**Dose**
The dose of Ibiamox® to treat an individual infection should take into account of:
- the expected pathogens and their likely susceptibility to the antibacterial agents (*see section 4.1*). Ibiamox® may be useful in instituting therapy prior to bacteriology; however, bacteriological studies should be performed to determine the causative organisms and their sensitivity to Ibiamox®
- the severity and the site of the infection
- the age, weight and renal function of the patient.

Duration of therapy should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.

It is recommended that any infection caused by haemolytic streptococci is treated for at least 10 days to prevent the occurrence of rheumatic fever or glomerulonephritis.

**Treatment of Infections**

*Adults and children >20kg*

<table>
<thead>
<tr>
<th>Indications*</th>
<th>Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper respiratory tract infections</strong>&lt;br&gt;(Due to streptococci, pneumococci, non-penicillinase-producing staphylococci and H. influenzae)</td>
<td>250mg every 8 hours.</td>
</tr>
<tr>
<td><strong>Lower respiratory tract infections</strong>&lt;br&gt;(Due to streptococci, pneumococci, non-penicillinase-producing staphylococci and H. influenzae)</td>
<td>500mg every 8 hours.</td>
</tr>
<tr>
<td><strong>Genito-urinary tract infections</strong>&lt;br&gt;(Due to Escherichia coli, Proteus mirabilis and Strep. faecalis)</td>
<td>250mg every 8 hours.</td>
</tr>
<tr>
<td><strong>Skin and soft tissue infections</strong>&lt;br&gt;(Due to streptococci, sensitive staphylococci and Escherichia coli)</td>
<td>250mg every 8 hours.&lt;br&gt;Or 500mg every 8 hours in severe infections or those caused by less susceptible organisms</td>
</tr>
</tbody>
</table>

* Consideration should be given to the official treatment guidelines for each indication.
Paediatric population

*Children <20kg*

<table>
<thead>
<tr>
<th>Indications*</th>
<th>Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper respiratory tract infections</strong>&lt;br&gt;(Due to streptococci, pneumococci, non-penicillinase-producing staphylococci and H. influenzae)</td>
<td>25mg/kg/day in equally divided doses every 8 hours.</td>
</tr>
<tr>
<td><strong>Lower respiratory tract infections</strong>&lt;br&gt;(Due to streptococci, pneumococci, non-penicillinase-producing staphylococci and H. influenzae)</td>
<td>50mg/kg/day in equally divided doses every 12 hours.</td>
</tr>
<tr>
<td><strong>Genito-urinary tract infections</strong>&lt;br&gt;(Due to Escherichia coli, Proteus mirabilis and Strep. faecalis)</td>
<td>25mg/kg/day in equally divided doses every 8 hours.</td>
</tr>
<tr>
<td><strong>Skin and soft tissue infections</strong>&lt;br&gt;(Due to streptococci, sensitive staphylococci and Escherichia coli)</td>
<td>25mg/kg/day in equally divided doses every 8 hours. Or 50mg/kg/day in equally divided doses every 8 hours in severe infections or those caused by less susceptible organisms</td>
</tr>
</tbody>
</table>

The children’s dose is intended for individuals whose weight will not cause dosage to be calculated greater than that recommended for adults.

* Consideration should be given to the official treatment guidelines for each indication.

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**Endocarditis prophylaxis***

**Dental procedures:** a referral to the hospital is recommended for the following patients:
- Patients to be given general anaesthetics who have been given penicillin in the previous month.
- Patients to be given general anaesthetics who have prosthetic heart valve.
- Patients who have had one or more attacks of endocarditis.

**Adults***
Initially 1g Ibiamox® intramuscularly with gentamicin** intramuscularly, immediately prior to anaesthesia (if given) or 15 minutes prior to dental procedure.

**Children under 10 years***
Half adult dose plus gentamicin**.
Dental procedures: Prophylaxis for patients undergoing extraction, scaling or surgery involving gingival tissues, and who have not received penicillin in the previous month and patients having general anaesthetic in whom oral antibiotics are considered inappropriate.

| Adults*  |
| 1g Ibiamox® intramuscularly immediately before induction, followed by 500mg oral amoxicillin six hours later. |
| Children under 10 years* |
| Half adult dose |

* Consideration should be given to the official treatment guidelines for each indication.
** Consult the appropriate data sheet for full prescribing information on gentamicin. Ibiamox® and gentamicin should not be mixed in the same syringe.

**Elderly population**
No dose adjustment is needed. Special attention to dosage is necessary if there is an overt renal dysfunction (see section 4.4).

**Renal impairment**
In renal impairment the excretion of the antibiotic will be delayed, and depending on the degree of impairment, it may be necessary to reduce the total daily dosage.

**Hepatic impairment**
Hepatically impaired patients should be dosed with caution and hepatic function should be monitored at a regular interval.

**Method of Administration**

**Intravenous**
Ibiamox® may be administered either by slow intravenous injection over a period of 3 to 4 minutes or via infusion over a period of 30 to 60 minutes.

**Intramuscular**
Ibiamox® is administered as a bolus dose.

For instructions on reconstitution and preparation before administration, see section 6.6.

**4.3. Contraindications**
Amoxicillin is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

Amoxicillin is contraindicated in patients with a hypersensitivity to the active substance, beta-lactam antibiotics or any of the excipients listed in section 6.1.
4.4. Special warnings and precautions for use

**Hypersensitivity reactions**
Amoxicillin should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Before commencing therapy with any penicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, cephamycins or penicillamine (*see sections 4.3 and 4.8*). Caution should also be taken in patients with a history of allergy, such as eczema, asthma, hay fever and hives. If any allergic reaction occurs, appropriate therapy should be instituted and amoxicillin therapy should be discontinued.

Serious anaphylactoid reactions require emergency treatment with adrenaline, oxygen and intravenous steroids. Airway management including tubation should also be administered as indicated.

**Electrolytes**
Massive doses of amoxicillin can cause hypokalaemia and sometimes hypernatraemia. Use of a potassium-sparing diuretic may be helpful. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts and renal functions should be monitored.

**Pseudomembranous colitis**
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop severe and persistent diarrhoea during or after receiving amoxicillin. In this situation, even if *Clostridium difficile* is only suspected, administration of amoxicillin should be discontinued and appropriate treatment given.

**Prolonged therapy**
Periodic assessment of renal, hepatic and haematopoietic function should be made during prolonged therapy. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving aerobacter, pseudomonas or candida), the medicine should be discontinued and/or appropriate therapy instituted.

**Convulsions**
Convulsions may occur in patients with impaired renal function or in those receiving high doses.
Anticoagulants
Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.4 and 4.8).

Crystalluria
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see sections 4.8 and 4.9).

Skin reactions
The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (see section 4.8).

Ibiamox® should be given with caution to patients with infectious mononucleosis or lymphatic leukemia since they are especially susceptible to ampicillin induced skin rashes.

4.5. Interaction with other medicines and other forms of interaction

Probenecid
Probenecid decreases renal tubular secretion of penicillins when used concurrently, resulting in increased and more prolonged amoxicillin serum concentrations and prolonged elimination half-life.

Allopurinol
There has been a report of an increased incidence of skin rash on concurrent administration.

Oral Anticoagulants
Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.4 and 4.8).

Bacteriostatic Antibiotics
Since bacteriostatic agents such as chloramphenicol, erythromycin, sulfonamides or tetracyclines may interfere with the bactericidal effect of penicillins in the
treatment of meningitis or other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

**Methotrexate**
Penicillins reduce the excretion of methotrexate thereby increasing the risk of methotrexate toxicity.

**Interference with diagnostic tests**
Penicillins may interfere with:
- Urinary glucose test- due to high concentrations of amoxicillin in the urine.
- Coomb's tests- interferes with positive direct antiglobulin
- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test
- Liver enzymes- serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) concentrations may be increased
- Total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol concentrations may be transiently decreased following Ibiamox® administration to pregnant women.

**Oestrogen Containing Oral Contraceptives**
Concurrent administration with amoxicillin may decrease the effectiveness of oral contraceptives. Patients should be advised to use an alternative or additional method of contraception.

### 4.6. Fertility, pregnancy and lactation

**Pregnancy**
Safety for use in pregnancy has not been established. Amoxicillin is known to diffuse across the placenta. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

**Breast-feeding**
Trace quantities of penicillin can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidiasis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued.

**Fertility**
No information is held on the effects on fertility.

### 4.7. Effects on ability to drive and use machines
During treatment with Ibiamox, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions) which may influence the ability to drive and use
machines. Patients should be cautious when driving or operating machinery (see section 4.8).

4.8. Undesirable effects
The following convention has been used to classify the occurrence of undesirable effects.

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>(≥1/10)</td>
<td>(≥1/100 to &lt;1/10)</td>
<td>(≥1/1,000 to &lt;1/100)</td>
<td>(≥1/10,000 to &lt;1/1,000)</td>
<td>(&lt;1/10,000)</td>
<td>(cannot be estimated from the available data)</td>
</tr>
</tbody>
</table>

### Blood and Lymphatic System Disorders

| Very rare | Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (see section 4.4). |

### Immune system disorders

| Very rare | As with other antibiotics, severe allergic reactions, including angioneurotic oedema, anaphylaxis (see section 4.4), serum sickness and hypersensitivity vasculitis If a hypersensitivity reaction is reported, the treatment must be discontinued. |

### Nervous system disorders

| Very rare | Hyperkinesia, dizziness and convulsions (see section 4.4). |
| Unknown | Encephalopathy has been reported and can be fatal |

### Infections and Infestations

| Very rare | Mucocutaneous candidiasis |

### Gastrointestinal disorders

| Common | Diarrhoea and nausea. |
| Uncommon | Vomiting. |
| Very rare | Antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis). Black hairy tongue. Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing |

### Hepato-biliary disorders

| Very rare | Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT. The significance of a rise in AST and/or ALT is unclear. |

### Skin and subcutaneous tissue disorders

| Common | Skin rash. |
| Uncommon | Urticaria and pruritus. |
Very rare

Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP) (See section 4.4).

Unknown

Other skin reactions include maculopapular rashes, morbilliform rash, drug eruption, erythema nodosum and pemphigoid reactions

Renal and Urinary tract disorders

Very rare

Interstitial nephritis, crystalluria

The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.

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**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions [https://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/)

**4.9. Overdose**

**Symptoms**
Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) leading to a disturbance of fluid and electrolyte balance may be evident. Problems are unlikely if adequate fluid is maintained but crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses (see sections 4.4 and 4.8). Obvious overdose will produce very high urinary concentrations, particularly after parenteral administration.

**Treatment**
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin may be removed by haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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**5. PHARMACOLOGICAL PROPERTIES**

**5.1. Pharmacodynamic properties**

**Pharmacotherapeutic Group:** Beta-lactam antibacterials, penicillins with extended spectrum  
**ATC code:** J01CA04
Mechanism of action
Amoxicillin binds to and inactivates penicillin-binding proteins (PBPs) located on the inner membrane of the bacterial cell wall. Inactivation of PBPs interferes with the cross-linkage of peptidoglycan chains necessary for bacterial cell wall strength and rigidity. This interrupts bacterial cell wall synthesis, which weakens the cell wall and causes cell lysis.

Like benzylpenicillin, amoxicillin is bactericidal against sensitive organisms during the stage of active multiplication.

In-vitro, amoxicillin differs from benzylpenicillin in the gram-negative spectrum. Amoxicillin has the same gram-positive and gram-negative spectrum as ampicillin.

In-vitro, most strains of Haemophilus influenzae, Neisseria gonorrhoea, Neisseria meningitidis, Escherischia coli, Proteus mirabilis and Salmonellae are sensitive to amoxicillin at serum concentrations, which may be expected following the recommended doses.

Strains of gonococci which are relatively resistant to benzylpenicillin may be sensitive to amoxicillin. In-vitro studies have also demonstrated the sensitivity of most strains of the following gram-positive bacteria: alpha- and beta-haemolytic streptococci, Streptococcus pneumoniae, non-penicillinase-producing staphylococci and Streptococcus faecalis.

However, some of the organisms were sensitive to amoxicillin only at concentrations achieved in the urine. Amoxicillin is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of pseudomonas and most strains of klebsiella and aerobacter are resistant.

5.2. Pharmacokinetic properties

Absorption
Amoxicillin is well absorbed after intra-muscular administration of any of the injection potencies, the relative bioavailability versus intravenous injection ranging from 73.2 – 96.7%.

Distribution
Amoxicillin is widely distributed to most body tissues and fluids. It penetrates well into purulent and mucoid sputum and into the middle ear. Penetration into cells, the eye and the cerebral spinal fluid is poor. However, inflammation of the meninges increases the amount of amoxicillin that crosses the blood brain barrier.
Amoxicillin is not highly protein-bound, being only 18% protein-bound in serum.

**Metabolism**
Small amount of amoxicillin is metabolised by hydrolysis to the inactive penicilloic acid, which is partly excreted in the urine.

**Elimination**
The half-life of amoxicillin is 61.3 minutes with normal renal function. About 75% of a 1g dose is excreted in the urine in 6 hours in the presence of normal renal function. 60% of this is unchanged and is excreted by glomerular filtration and tubular secretion, while 15% is amoxicillin’s inactive metabolite (penicilloic acid). The amount of amoxicillin found in the bile is variable depending on normal biliary secretory function.

**Age**
The elimination half-life of Ibiamox® is prolonged in neonates and the elderly due to incomplete or decreased renal function.

**Renal impairment**
In renal impairment the excretion of the antibiotic will be delayed *(see section 4.2).*

**5.3. Preclinical safety data**
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

**6. PHARMACEUTICAL PARTICULARS**

**6.1. List of excipients**
None

**6.2. Incompatibilities**
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Ibiamox® should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.
If prescribed concomitantly with an aminoglycoside (such as gentamicin), the antibiotics should not be mixed in the same syringe or intravenous fluid container due to loss of activity of the aminoglycoside under these conditions.

6.3. Shelf life
36 months

6.4. Special precautions for storage
Store at or below 25°C
Protect from moisture and light.

When prepared for intramuscular or direct intravenous injection, Ibiamox® should be administered immediately or within 1 hour after reconstitution. When prepared for infusions, Ibiamox® should be administered within 1 hour, even though Ibiamox® maintains a satisfactory degree of activity at room temperature in various infusion fluids see section 6.6.

6.5. Nature and contents of container
Ibiamox® 250mg or 500mg or 1000mg injections are in glass vials in pack sizes of 1 vial or 10 vials. Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling
Reconstitution of vials: mix with diluent and shake vigorously. Check for absence of particulate matter before use.

A transient pink colouration or slight opalescence may appear during reconstitution with water for injection. Reconstituted solutions are normally a pale straw colour.

Intravenous Injection
Reconstitute with 5mL of water for injection and shake immediately after adding the diluent. When giving part doses refer to the section on reconstitution of part doses.

Intravenous Infusion
Reconstitute as per Intravenous Injection above and add to infusion fluid as follows:

<table>
<thead>
<tr>
<th>Intravenous Fluids</th>
<th>Stability Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride (normal saline)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Compound sodium chloride (Ringer's solution)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Sodium lactate</td>
<td>3 hours</td>
</tr>
<tr>
<td>Compound sodium lactate (Hartmann's solution)</td>
<td>3 hours</td>
</tr>
<tr>
<td>Dextrose (5%)</td>
<td>1 hour</td>
</tr>
<tr>
<td>Sodium chloride and (4%) dextrose</td>
<td>1 hour</td>
</tr>
</tbody>
</table>
Ibiamox is compatible with commonly used intravenous solutions. However, it is relatively less stable in carbohydrate solutions. It is preferable to avoid using them.

**Intramuscular Injection**
Preparation: Reconstitute with water for injections. Shake immediately after adding the diluent. Add 2mL to 250mg and 500mg vials and 4mL to 1g vial and inject the total volume produced.

If pain is experienced on intramuscular injection, a sterile 1% solution of lignocaine hydrochloride or 0.5% solution of procaine hydrochloride may be used in place of water for injections.

**Reconstitution of part doses:**
The dry powder in the vial displaces a set volume once it is in solution, therefore this must be allowed for by calculating the volume of diluent to be added to ensure the correct dose is given.
- 250mg of stated activity displaces 0.2mL of diluent.
- 500mg of stated activity displaces 0.4mL of diluent.
- 1000mg of stated activity displaces 0.8mL of diluent.

For example: Add 4.8mL of diluent to a 250mg vial to produce: 250mg in 5mL, 200mg in 4mL, 150mg in 3mL, 100mg in 2mL, 50mg in 1mL. Similarly, add 4.6mL of diluent to a 500mg vial to produce 500mg in 5mL solution.

When the whole vial dose is to be given either add 5mL and withdraw and administer the entire contents or calculate the displacement and add a lesser volume of 5mL.

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

7. **MEDICINE SCHEDULE**
   Prescription Medicine

8. **SPONSOR**
   Douglas Pharmaceuticals Ltd
   P O Box 45 027
   Auckland 0651
   New Zealand
9. DATE OF FIRST APPROVAL
09 December 1982

10. DATE OF REVISION OF THE TEXT
30 May 2017

Summary table of changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sections</td>
<td>Update to the SmPC format including reformatting and re-ordering of existing information</td>
</tr>
<tr>
<td>4.3</td>
<td>Added/updated contraindication on cross-reactivity</td>
</tr>
<tr>
<td>4.4</td>
<td>Updated safety information on potential cross-reactivity, electrolyte imbalance, pseudomembranous colitis, oral anticoagulant and skin reaction.</td>
</tr>
<tr>
<td>4.5</td>
<td>Updated safety information on the interaction with oral anticoagulants, methotrexate and interference with diagnostic tests</td>
</tr>
<tr>
<td>4.7</td>
<td>Updated safety information on the effects on ability to operate machinery</td>
</tr>
<tr>
<td>4.9</td>
<td>Added information on overdose</td>
</tr>
<tr>
<td>5.1</td>
<td>Added information on the mechanism of action</td>
</tr>
<tr>
<td>5.2</td>
<td>Clarified pharmacokinetic information</td>
</tr>
<tr>
<td>5.3</td>
<td>Clarified preclinical safety data</td>
</tr>
</tbody>
</table>