AUSTRALIAN PRODUCT INFORMATION- MEROPENEM KABI (MEROPENEM (AS TRIHYDRATE))

1 NAME OF THE MEDICINE

Meropenem, as meropenem trihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Meropenem Kabi powder for intravenous injection contains meropenem trihydrate equivalent to meropenem, 500 mg or 1 g, blended with sodium carbonate. Meropenem Kabi contains 208 mg sodium carbonate for each gram of meropenem (anhydrous potency). It contains no preservative.

Meropenem Kabi powder for intravenous injection or infusion		**500 mg**	**1 g**
Active ingredient	Meropenem (as trihydrate)	570 mg	1.14 g
	equivalent to anhydrous meropenem	500 mg	1 g
Excipient	Sodium carbonate	104 mg	208 mg

3 PHARMACEUTICAL FORM

Meropenem Kabi is presented as a sterile white or light yellow powder for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Meropenem Kabi is indicated for treatment of the following infections, in adults and children (aged 3 months and over), when the causative organisms are known or suspected to be resistant to commonly used antibiotics:

- Community acquired lower respiratory tract infection
- Hospital acquired lower respiratory tract infection
- Complicated urinary tract infection
- Febrile neutropenia
- Intra-abdominal and gynaecological (poly microbial) infections
- Complicated skin and skin structure infections
- Meningitis
- Septicaemia

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Usual dose

500 mg to 1 g by intravenous administration every 8 hours depending on type and severity of infection, the known or suspected susceptibility of the pathogen(s) and the condition of the patient.

Exceptions

1. Febrile episodes in neutropenic patients - the dose should be 1 g every 8 hours.
2. Meningitis - the dose should be 2 g every 8 hours.

As with other antibiotics, caution may be required in using meropenem as monotherapy in critically ill patients with known or suspected Pseudomonas aeruginosa lower respiratory tract infection.

Regular sensitivity testing is recommended when treating Pseudomonas aeruginosa infection.

Meropenem Kabi should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes (see **Section 4.2 Dose and method of administration**).

Dosage schedule for adults with impaired renal function

Dosage should be reduced in patients with creatinine clearance less than 51 mL/min, as scheduled below Table 1.

Table 1

Creatinine Clearance (mL/min)	Dose (based on unit doses of 500mg, 1g, 2g)	Frequency
26 to 50	One unit dose	Every 12 hours
10 to 25	One-half unit dose	Every 12 hours
<10	One-half unit dose	Every 24 hours

Meropenem is cleared by haemodialysis. If continued treatment with Meropenem Kabi is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with peritoneal dialysis.

Use in adults with hepatic insufficiency

No dosage adjustment is necessary in patients with impaired hepatic metabolism.

Elderly patients

No dosage adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 mL/min.

Children

For infants and children over 3 months and up to 12 years of age the recommended intravenous dose is 10 to 40 mg/kg every 8 hours depending on type and severity of infection, the known or suspected susceptibility of the pathogen(s) and the condition of the patient. In children over 50 kg weight, adult dosage should be used.

Exceptions

1. Febrile episodes in neutropenic patients - the dose should be 20 mg/kg every 8 hours.
2. Meningitis - the dose should be 40 mg/kg every 8 hours.

Meropenem Kabi should be given as an IV bolus over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes.

There is no experience in children with renal impairment.

Method of administration

Meropenem Kabi to be used for bolus intravenous injection should be reconstituted with sterile Water for Injections (10 mL per 500 mg meropenem). This provides an approximate available concentration of 50 mg/mL. Reconstituted solutions are both clear and colourless to pale yellow.

Meropenem Kabi for intravenous infusion may be directly reconstituted with a compatible infusion fluid and then further diluted (50 to 200 mL) with the compatible infusion fluid.

Shake reconstituted solution before use. All vials are for single use in one patient only. Discard any residue. Standard aseptic technique should be employed during reconstitution and administration.

Compatibility

Meropenem Kabi is compatible with the following infusion fluids:

- 0.9% sodium chloride intravenous infusion
- 5% or 10% glucose intravenous infusion
- 5% glucose intravenous infusion with 0.02% sodium bicarbonate
- 0.9% sodium chloride and 5% glucose intravenous infusion
- 5% glucose with 0.225% sodium chloride intravenous infusion
- 5% glucose with 0.15% potassium chloride intravenous infusion
- 2.5% and 10% mannitol intravenous infusion
- normosol-M in 5% glucose intravenous infusion

Stability

Meropenem Kabi should not be mixed with or physically added to solutions containing other drugs.

After reconstitution:

The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed one hour.

Solutions of Meropenem Kabi should not be frozen.

4.3 CONTRAINDICATIONS

Meropenem is contraindicated in patients who have demonstrated hypersensitivity to this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified Precautions

Hypersensitivity reaction (allergic/anaphylaxis)

Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving therapy with β-lactams. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity when treated with another β-lactam. Before initiating treatment with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, or other β-lactam antibiotics. If an allergic reaction occurs to meropenem then discontinue the medicine. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

As with other antibiotics, overgrowth of non-susceptible organisms may occur and repeated evaluation of each patient is necessary.

As with other β-lactam antibiotics, strains of *Pseudomonas aeruginosa* may develop resistance on treatment with meropenem. Development of resistance has been reported in pseudomonal hospital acquired lower respiratory tract infections. In such cases, meropenem should be used with caution and repeat sensitivity testing is recommended.

Gastrointestinal disease

History of colitis: Antibiotics should be prescribed with care for individuals with a history of gastrointestinal disease, especially ulcerative colitis, regional enteritis, or antibiotic associated colitis.

Pseudomembranous colitis

Rarely, pseudomembranous colitis has been reported with meropenem as with practically all antibiotics and may vary in severity from slight to life-threatening. Therefore, antibiotics should be prescribed with care for individuals with a history of gastrointestinal complaints, particularly colitis. It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea when using an antibiotic. Although studies indicate that a toxin produced by *Clostridium difficile* is one of the main causes of antibiotic-associated colitis, other causes should be considered. Mild cases usually respond to medicine discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered.

Fluids, electrolytes and protein replacement should be provided when indicated. Medicines which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition and should not be used.

Seizures have infrequently been reported during treatment with carbapenems, including meropenem.

Use in Severe Meningitis

Neurological sequelae were reported following treatment of severe meningitis with meropenem. In clinical trials these adverse events were reported in 23 of 148 patients treated with meropenem and in 17 of 144 patients treated with comparator antibiotics.

Use with Valproic Acid/Sodium Valproate

The concomitant use of valproic acid/sodium valproate and meropenem is not recommended. Meropenem may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

Skin and subcutaneous tissue disorders

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem (see **Section 4.8 Adverse Effects (Undesirable Effects)**). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Use in hepatic impairment

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytosis). Patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem.

Use in renal impairment

See **Section 4.2 Dose and method of administration**.

Use in the elderly

See **Sections 4.2 Dose and method of administration** and **5.2 Pharmacokinetic Properties**.

Paediatric use

Efficacy and tolerability in infants under 3 months of age have not been established; therefore, meropenem is not recommended for use below this age.

Effects on laboratory tests

A positive or indirect Coombs' test may develop.

Sodium

This medicinal product contains sodium which should be taken into consideration for patients on a controlled sodium diet.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Meropenem has been administered concomitantly with many other medications without apparent adverse interaction. However, no specific medicine interaction studies other than with probenecid were conducted.

Probenecid

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. As the potency and duration of action of meropenem dosed without probenecid are adequate the co-administration of probenecid with meropenem is not

recommended. The potential effect of meropenem on the protein binding of other medicines or metabolism has not been studied. However, the protein binding is so low (approximately 2%) that no interactions with other compounds would be expected on the basis of this mechanism.

Valproic acid/sodium valproate

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60 to 100% decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of meropenem in patients stabilised on valproic acid/sodium valproate is not considered to be manageable and therefore should be avoided (see **Sections 4.4 Special warnings and precautions for use** and **6.2 Incompatibilities**).

The concomitant use of meropenem and valproic acid/sodium valproate/valpromide is not recommended.

Oral anticoagulants

Simultaneous administration of antibiotics with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant agents, including warfarin, in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anticoagulant agent.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility was not impaired in rats with exposures (based on AUC) slightly greater than those observed in patients at the recommended intravenous dose.

Use in pregnancy (Category B2)

Reproduction studies conducted with meropenem in rats have shown no embryotoxicity or teratogenicity at plasma exposures (based on AUC values) approximately equal to those observed in patients at the recommended intravenous dose. In a teratology study in cynomolgus monkeys given daily intravenous injections meropenem showed no evidence of teratogenicity at dose levels up to 360 mg/kg/day.

There are however, no adequate or well controlled trials of meropenem in pregnant women. Because reproduction studies are not always predictive of human response, meropenem should not be used in pregnancy unless the potential benefit justifies the potential risk to the fetus.

Use in lactation

Meropenem should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby. Meropenem has been reported to be excreted in human breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the ability to drive and use machines have been performed. However, when driving or operating machines it should be taken into account that headache, paraesthesiae and convulsions have been reported for meropenem.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Meropenem is generally well tolerated.

In clinical trials, adverse events lead to cessation of treatment in less than 1% of patients. Serious adverse events are rare.

Table 2- Common events	
General disorders and administration site conditions	Inflammation, thrombophlebitis, pain.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain.
Blood and lymphatic system disorders	Thrombocythaemia.
Nervous system disorders	Headache.
Skin and subcutaneous tissue disorders	Rash, pruritus, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.
Hepatobiliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphate increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, and blood bilirubin increased alone or in combination have been reported.

Table 3- Adverse reactions reported at a frequency <1%	
Immune system disorders	Systemic allergic reactions (hypersensitivity) may occur following administration of meropenem. These reactions may include angioedema and manifestations of anaphylaxis.
Skin and subcutaneous tissue disorders	Urticaria (uncommon). Severe skin reactions, such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been observed. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome), acute generalised exanthematous pustulosis (AGEP) (not known).
Gastrointestinal disorders	Pseudomembranous colitis.
Hepatobiliary disorders	Jaundice and hepatic failure have been reported but a causal link with meropenem has not been established.
Blood and lymphatic system disorders	Uncommon - Eosinophilia, leucopaenia, thrombocytopaenia and neutropenia; Rare - agranulocytosis; Very rare - haemolytic anaemia. A positive direct or indirect Coombs' test may develop.
Cardiac disorders	Cardiac failure has been reported but a causal link with meropenem has not been established.
Nervous system disorders	Uncommon — paraesthesiae, convulsions.
Psychiatric disorders	Delirium and hallucinations have been reported but a causal link with meropenem has not been established.

Respiratory, thoracic and mediastinal disorders	Pneumonia and respiratory failure have been reported but a causal link with meropenem has not been established. Pneumonia has been reported but a causal link with meropenem has not been established.
Renal and urinary disorders	Renal impairment.
Whole body	Fever and sepsis have been reported but a causal link with meropenem has not been established.
Infections and infestations	Oral and vaginal candidiasis (uncommon).

Reporting suspected adverse effects

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 at www.tga.gov.au/safety/reporting-problems.

4.9 OVERDOSE

The pharmacological properties and mode of administration make it unlikely that intentional overdose will occur. Accidental overdosage could occur during therapy, particularly in patients with renal impairment. Treatment of overdosage should be symptomatic. In normal individuals rapid renal elimination will occur. In subjects with renal impairment haemodialysis will remove meropenem and its metabolite.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Meropenem is a carbapenem antibiotic for parenteral use, that is stable to human dehydropeptidase-1 (DHP-1).

Microbiology

Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis. The ease with which it penetrates bacterial cell walls, its high level of stability to all serine β-lactamases and its marked affinity for the Penicillin Binding Proteins (PBPS) explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria. Bactericidal concentrations are commonly the same as the minimum inhibitory concentrations (MICs).

Meropenem is stable in susceptibility tests and these tests can be performed using normal routine methods. *In vitro* tests show that meropenem acts synergistically with various antibiotics. It has been demonstrated both *in vitro* and *in vivo* that meropenem has a post-antibiotic effect.

Meropenem is usually active, in vitro and in clinical infections, against the strains of bacteria shown below:

Gram-positive aerobes

Enterococcus faecalis, Staphylococcus aureus (penicillinase negative and positive), Staphylococci-coagulase-negative including *Staphylococcus epidermidis*, streptococci including *Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus mitis, Streptococcus milleri, Streptococcus sanguis, Streptococcus viridans*.

Gram-negative aerobes

Acinetobacter anitratus, Citrobacter spp., including *Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae*, and other *Enterobacter* spp., *Escherichia coli*, *Haemophilus influenzae* (including β-lactamase positive strains), *Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, Neisseria meningitidis, Klebsiella pneumoniae*, and other *Klebsiella* spp., *Morganella morganii, Proteus mirabilis, Serratia* spp.

Anaerobic bacteria

Bacteroides fragilis, Bacteroides thetaiotaomicron, and other *Bacteroides* spp., *Clostridium* spp. including *C. perfringens, Eubacterium lentum, Fusobacterium* spp., *Mobiluncus curtisii, Peptostreptococcus* spp., *Peptococcus* spp.

Some strains of *Pseudomonas aeruginosa* are susceptible to meropenem *in vitro* and in clinical infections.

Enterococcus faecium, Stenotrophomonas (Xanthomonas) maltophilia, and methicillin resistant staphylococci have been found to be resistant to meropenem.

Disc Susceptibility

Dilution of diffusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method, (e.g. NCCLS). Standard susceptibility test procedure require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable, other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A 30 minute intravenous infusion of a single dose of meropenem in normal volunteers results in peak plasma levels of approximately 11 µg/mL for the 250 mg dose, 23 µg/mL for the 500 mg dose, 49 µg/mL for the 1 g dose and 115 µg/mL following the 2 g dose.

A 5 minute intravenous bolus injection of meropenem in normal volunteers results in peak plasma levels of approximately 52 µg/mL for the 500 mg dose and 112 µg/mL for the 1 g dose.

Intravenous infusions over 2 minutes, 3 minutes and 5 minutes of a 1 g dose of meropenem were compared in a three-way crossover trial. These durations of infusion resulted in peak plasma levels of 110, 91 and 94 µg/mL, respectively.

Distribution

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.

Plasma protein binding of meropenem is approximately 2%.

Metabolism

The only metabolite of meropenem is microbiologically inactive.

Excretion

After an intravenous dose of 500 mg, plasma levels of meropenem decline to values of 1 µg/mL or less, 6 hours after administration.

When multiple doses are administered at 8 hourly intervals to subjects with normal renal function, accumulation of meropenem does not occur.

In subjects with normal renal function, meropenem's elimination half-life is approximately one hour.

Approximately 70% of the intravenous administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/mL are maintained for up to 5 hours at the 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

Special Populations

<u>Use in hepatic impairment</u>

Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

<u>Use in renal impairment</u>

Pharmacokinetic studies in patients with renal insufficiency have shown the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment.

Use in the elderly

Pharmacokinetic studies in the elderly have shown a reduction in plasma clearance of meropenem which correlated with age-associated reduction in creatinine clearance.

Paediatric use

Studies in children have shown that the pharmacokinetics of meropenem in children are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in children under the age of 2 years.

The pharmacokinetics are linear over the dose range of 10 to 40 mg/kg.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Meropenem, with and without metabolic activation as appropriate, was not genotoxic in assays for gene mutations (*Salmonella typhimurium*, *E. coli* and Chinese hamster ovary cells) and chromosomal damage (mouse micronucleus assay and human lymphocytes *in vitro*).

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium carbonate.

6.2 INCOMPATIBILITIES

Meropenem Kabi should only be mixed with products listed within **Section 4.2 Dose and method of administration**. See also **Section 4.5 Interactions with other medicines and other forms of interactions**.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Prior to reconstitution, store Meropenem Kabi powder for intravenous injection packs below 25°C. See **Section 4.2 Dose and method of administration** for storage of prepared solutions.

6.5 NATURE AND CONTENTS OF CONTAINER

Meropenem Kabi is a white to light yellow powder in clear 20 mL glass vials, closed with bromobutyl rubber closures, sealed with aluminium caps with polypropylene disc (violet for 500 mg and grey for 1 g), containing meropenem trihydrate 570 mg (equivalent to meropenem 500 mg) or meropenem trihydrate 1.14 g (equivalent to meropenem 1.00 g).

Meropenem Kabi 500 mg (AUST R 196965) and Meropenem Kabi 1 g (AUST R 196966) is available in packs of 1 or 10 vials.

* not all pack sizes may be marketed.

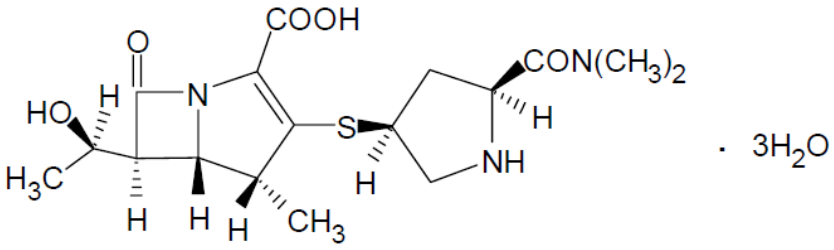
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:

Meropenem trihydrate has the following structural formula:



CAS Number: 119478-56-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Fresenius Kabi Australia Pty Limited
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Australia
Telephone: 1300 732 001

9 DATE OF FIRST APPROVAL

25 Mar 2013

10 DATE OF REVISION OF THE TEXT

6 Jun 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Revised contraindications section.
4.4	Updated safety information including hypersensitivity reaction with valproic acid/sodium valproate.
4.5	Revised safety information for valproic acid/sodium valproate.
4.6	Revised safety data for lactation.
4.8	Added renal impairment, delirium & hallucinations as adverse reactions. Updated adverse reaction information for skin & subcutaneous tissue disorders.
2, 3, 4, 5, 6, 7 & 8	Minor editorial changes.