

## DATA SHEET

# MEROPENEM RANBAXY

Meropenem, as the trihydrate.

### **Presentation**

Meropenem powder for injection or infusion is a white to pale yellow crystalline sterile powder for reconstitution containing meropenem trihydrate equivalent to anhydrous meropenem 500 mg or 1 g and the inactive ingredient sodium carbonate anhydrous 104 mg or 208 mg respectively. The pH of freshly constituted solutions is between 7.3 and 8.3.

### **Uses**

#### **Actions**

Meropenem is a carbapenem antibiotic for parenteral use, that is stable to human dehydropeptidase-I (DHP-I). It is structurally similar to imipenem.

Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis.

The ease with which it penetrates bacterial cells, its high level of stability to most serine  $\beta$ -lactamases and its high affinity for the Penicillin Binding Proteins (PBPs) explain the potent bactericidal activity of meropenem against a broad spectrum of aerobic and anaerobic bacteria. The bactericidal concentrations are generally within one doubling dilution of the minimum inhibitory concentrations (MICs).

Meropenem is stable in susceptibility tests and these tests can be performed using the normal routine systems. *In vitro* tests show that meropenem can act synergistically with various antibiotics. It has been demonstrated both *in vitro* and *in vivo* that meropenem has a post-antibiotic effect against Gram-positive and Gram-negative organisms.

#### **Mechanism of resistance**

Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of  $\beta$ -lactamases that can hydrolyse carbapenems.

Localised cluster of infections due to carbapenem-resistant bacteria have been reported in some regions.

The susceptibility to meropenem of a given clinical isolate should be determined by standard methods. Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

The antibacterial spectrum of meropenem includes the following species, based on clinical experience and therapeutic guidelines.

#### **Commonly susceptible species: Gram-positive aerobes**

*Enterococcus faecalis* (note that *E. faecalis* can naturally display intermediate

susceptibility), *Staphylococcus aureus* (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSA are resistant to meropenem), *Staphylococcus* species including *Staphylococcus epidermidis* (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSE are resistant to meropenem), *Streptococcus agalactiae* (Group B streptococcus), *Streptococcus milleri* group (*S. anginosus*, *S. constellatus*, and *S. intermedius*), *Streptococcus pneumoniae*, *Streptococcus pyogenes* (Group A streptococcus).

**Commonly susceptible species: Gram-negative aerobes**

*Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Neisseria meningitidis*, *Proteus mirabilis*, *Proteus vulgaris*, *Serratia marcescens*.

**Commonly susceptible species: Gram-positive anaerobes**

*Clostridium perfringens*, *Peptoniphilus asaccharolyticus*, *Peptostreptococcus* species (including *P. micros*, *P. anaerobius*, *P. magnus*).

**Commonly susceptible species: Gram-negative anaerobes**

*Bacteroides caccae*, *Bacteroides fragilis* group, *Prevotella bivia*, *Prevotella disiens*.

Species for which acquired resistance may be a problem: Gram-positive aerobes *Enterococcus faecium* (*E. faecium* can naturally display intermediate susceptibility even without acquired resistance mechanisms; note that in some European countries the frequency of resistance among *E. faecium* is greater than 50 % of isolates).

**Species for which acquired resistance may be a problem: Gram-negative aerobes**

*Acinetobacter* species, *Burkholderia cepacia*, *Pseudomonas aeruginosa*.

**Inherently resistant organisms: Gram-negative aerobes**

*Stenotrophomonas maltophilia*, *Legionella* species.

**Other inherently resistant organisms**

*Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Coxiella burnetii*, *Mycoplasma pneumoniae*.

The published medical microbiology literature describes in-vitro meropenem-susceptibilities of many other bacterial species. However the clinical significance of such in-vitro findings is uncertain. Advice on the clinical significance of in-vitro findings should be obtained from local infectious diseases and clinical microbiology experts and local professional guidelines.

meropenem and imipenem have a similar profile of clinical utility and activity against multiresistant bacteria. However, meropenem is intrinsically more potent against *Pseudomonas aeruginosa* and may be active *in vitro* against imipenem-resistant strains.

Meropenem is active *in vitro* against many strains resistant to other b-lactam antibiotics.

This is explained in part by enhanced stability to b-lactamases. Activity *in vitro* against strains resistant to unrelated classes of antibiotics such as aminoglycosides or quinolones is common.

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.

## **Pharmacokinetics**

In healthy subjects the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l/kg (11.27 l) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean Cmax values of approximately 23, 49 and 115 µg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 µg.h/ml. After infusion over 5 minutes Cmax values are 52 and 112 µg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.

A study of 12 patients administered meropenem 1000 mg 8 hourly post-surgically for intraabdominal infections showed a comparable Cmax and half-life to normal subjects but a greater volume of distribution 27 L.

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

## **Distribution**

The average plasma protein binding of meropenem was approximately 2% and was independent of concentration. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynaecological tissues, skin, fascia, muscle, and peritoneal exudates.

## **Metabolism**

Meropenem is metabolised by hydrolysis of the b-lactam ring generating a microbiologically inactive metabolite. *In vitro* meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor.

## **Elimination**

Meropenem is primarily excreted unchanged by the kidneys; approximately 70 % (50 –75 %) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

## **Renal insufficiency**

Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold in severe impairment (CrCL 4-23 ml/min) and 10 fold in haemodialysis patients (CrCL<2 ml/min) when compared to healthy subjects (CrCL >80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment (see DOSAGE AND ADMINISTRATION).

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.

## **Hepatic Insufficiency**

A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.

## **Adult patients**

Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

## **Paediatrics**

The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed Cmax values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months t1/2 1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2-5 years), 5.3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months).

Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter-individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 %T>MIC for *P. aeruginosa* in 95 % of pre-term and 91 % of full term neonates.

## **Elderly**

Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment (see DOSAGE AND ADMINISTRATION).

## **Indications**

MEROPENEM RANBAXY is indicated for treatment, in adults and children, of the following infections caused by single or multiple susceptible bacteria and as empiric therapy prior to the identification of the causative organisms:

- Lower Respiratory Tract Infections
- Urinary Tract Infections, including complicated infections
- Intra-abdominal Infections
- Gynaecological Infections, including postpartum infections
- Skin and Skin Structure Infections
- Meningitis
- Septicaemia
- Empiric treatment, including initial monotherapy, for presumed bacterial infections in host-compromised, neutropenic patients

Because of its broad spectrum of bactericidal activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria, meropenem is effective for the treatment of polymicrobial infections.

## **Dosage and Administration**

### **A) Adults**

Dosage range is 1.5 g – 6 g daily in three divided doses.

#### **Usual dose**

500 mg to 1 g by intravenous administration every 8 hours depending on type and severity of infection, the known or expected 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 infections.

Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infections.

Meropenem should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes (see Method of Administration). There is limited safety data available to support the administration of a 2 g bolus dose.

## **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.

Creatinine Clearance (mL/min)	Dose (based on unit doses of 500 mg, 1 g, 2 g every 8 hours)	Frequency
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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 and haemofiltration. If continued treatment with meropenem is necessary, the unit dose (based on the type and severity of infection) is recommended at the completion of the haemodialysis procedure to re-institute effective treatment.

There is no experience with peritoneal dialysis.

### **Use In Adults With Hepatic Insufficiency**

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

### **B) Elderly**

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

### **C) 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 RANBAXY should be given as an IV bolus over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes. There is limited safety data available to support the administration of a 40 mg/kg bolus dose. There is no experience in children with renal impairment.

### **Method of Administration**

MEROPENEM RANBAXY to be used for bolus intravenous injection should be constituted with sterile water for injection (10 mL per 500 mg meropenem). This provides an approximate available concentration of 50 mg/mL. Constituted solutions are clear or pale yellow.

MEROPENEM RANBAXY for intravenous infusion may be directly constituted with a compatible infusion fluid (see COMPATIBILITY) and then further diluted (50 to 200 mL) with the compatible infusion fluid, as needed.

Displacement values:

500 mg vial: 0.4 ml

1 g vial: 0.9 ml

### **Compatibility**

MEROPENEM RANBAXY 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
- 5% glucose and 0.9% sodium chloride 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.

Also see SPECIAL PRECAUTIONS FOR STORAGE

MEROPENEM RANBAXY should not be mixed with or physically added to solutions containing other medicines.

Solutions of MEROPENEM RANBAXY should not be frozen.

### ***Contraindications***

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

### ***Warnings and Precautions***

Patients who have a history of hypersensitivity to carbapenems, penicillins or other b-lactam antibiotics may also be hypersensitive to MEROPENEM RANBAXY. As with all b-lactam antibiotics rare hypersensitivity reactions (serious and occasionally fatal) have been reported (see ADVERSE EFFECTS).

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

Rarely, pseudomembranous colitis has been reported with meropenem as with virtually all antibiotics; therefore, its diagnosis should be considered in patients who develop diarrhoea in association with the use of meropenem.

The concomitant use of valproic acid/sodium valproate and meropenem is not recommended (see INTERACTIONS). Meropenem may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.

A positive direct or indirect Coombs test may develop.

### ***Use In Children***

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

### ***Use In Patients With Renal Insufficiency***

See DOSAGE AND ADMINISTRATION.

### ***Use In Patients With Liver Disease***

Patients with pre-existing liver disorders should have liver function monitored during treatment with MEROPENEM RANBAXY.

## **Use In Pregnancy**

The safety of meropenem in human pregnancy has not been established, although animal studies have not shown an adverse effect on the developing foetus. Meropenem should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus.

## **Use In Lactation**

Meropenem is detectable at very low concentrations in animal breast milk. Meropenem should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

## **Effect On Ability To Drive Or Operate Machinery**

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, paraesthesia and convulsions have been reported for meropenem.

## **Adverse Effects**

Meropenem is generally well tolerated. Adverse reactions rarely lead to cessation of treatment.

Serious adverse reactions are rare.

The following adverse reactions have been identified following clinical studies with meropenem.

Their frequency is presented in Table 1 – Frequency of Adverse Reactions (data derived from clinical trial data sources) using CIOMS III frequency classification and then listed by MedDRA SOC and at the preferred level. Frequencies of occurrence of undesirable effects are defined as: very common ( $\geq 1/10$ ;  $\geq 10\%$ ); common ( $\geq 1/100$  to  $<1/10$ ;  $\geq 1\%$  to  $<10\%$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ;  $\geq 0.1\%$  to  $<1\%$ ); rare ( $\geq 1/10,000$  to  $<1/1,000$ ;  $\geq 0.01\%$  to  $<0.1\%$ ); very rare ( $<1/10,000$ ;  $<0.01\%$ ).

Table 1 – Frequency of Adverse Reactions (data derived from clinical trial data sources)<sup>1</sup>.

System Organ Class	Frequency	Reaction
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	thrombocythaemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia
Nervous system disorders	Common	headache
	Uncommon	parasthesiae
	Rare	convulsions

Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea
Hepatobiliary disorders	Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased.
	Uncommon	blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	urticaria
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis

<sup>1</sup> 1999 Norrby SR and Gildon KM. Safety Profile of Meropenem: a review of nearly 5000 patients treated with Meropenem.; Sand J Infect Dis 1999; 31: 3-10 and the integrated Summary of Safety 1993.

The following adverse reactions have been identified from post-marketing clinical trials and spontaneous reports. Their frequency is presented in Table 2 - Reporting Rate of Adverse Reactions (data derived from a combination of post-marketing clinical trial and spontaneous sources) using CIOMS III frequency classification and then listed by MedDRA SOC and at the preferred level. Frequencies of occurrence of undesirable effects are defined as: very common ( $\geq 1/10$ ;  $\geq 10\%$ ); common ( $\geq 1/100$  to  $<1/10$ ;  $\geq 1\%$  to  $<10\%$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ;  $\geq 0.1\%$  to  $<1\%$ ); rare ( $\geq 1/10,000$  to  $<1/1,000$ ;  $\geq 0.01\%$  to  $<0.1\%$ ); very rare ( $<1/10,000$ ;  $<0.01\%$ ).

Table 2 – Reporting Rate of Adverse Reactions (data derived from a combination of postmarketing clinical trial and spontaneous sources)

System Organ Class	Frequency	Reaction
Blood and lymphatic system disorders	Rare	agranulocytosis
	Very rare	haemolytic anaemia
Immune system disorders	Very rare	angioedema, manifestations of anaphylaxis.
Gastrointestinal disorders	Very rare	Pseudomembranous colitis
Skin and subcutaneous tissue disorders	Common	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

## ***Interactions***

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.

Meropenem has been administered concomitantly with many other medications without apparent adverse interaction. Meropenem may reduce serum valproic acid levels.

Subtherapeutic levels may be reached in some patients. However, no specific drug interaction studies other than with probenecid were conducted.

Decreases in serum valproic acid levels that may fall below the therapeutic range, have been reported in patients co-administered sodium valproate with carbapenem agents, including meropenem. The significant reductions in serum valproic acid levels (60-100%) have been reported within two days of carbapenem administration and may lead to inadequate seizure control. Due to the rapid onset and the extent of the decrease in serum levels, co-administration of carbapenem agents in patients stabilised on sodium valproate is not considered to be manageable and should therefore be avoided (See WARNINGS AND PRECAUTIONS).

## ***Overdosage***

Intentional overdosing of meropenem is unlikely, although overdosing could occur during therapy particularly in patients with renal impairment. Limited post-marketing experience indicates that if adverse events occur following overdosage, they are consistent with the adverse event profile described in ADVERSE EFFECTS, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered. In normal individuals rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

## ***Pharmaceutical Precautions***

### **Shelf-Life**

2 years

### **Special Precautions for Storage**

Prior to constitution, store MEROPELEM RANBAXY powder for intravenous injection or infusion packs below 25°C.

Freshly prepared solutions of MEROPELEM RANBAXY should be used whenever possible. However, constituted solutions of MEROPELEM RANBAXY as supplied in injection and infusion vials and constituted as described above, maintain satisfactory

potency at room temperature (up to 25°C) or under refrigeration (4°C) as shown in the following table:

Diluent	Hours stable	
	At 15- 25°C	4°C
Vials constituted with Water for Injections for bolus injection	8	24
Solutions 1 to 20 mg/mL prepared with 0.9% sodium chloride	8	48
5% glucose	3	14
5% glucose and 0.225% sodium chloride	3	14
5% glucose and 0.9% sodium chloride	3	14
5% glucose and 0.15% potassium chloride	3	14
2.5% or 10% mannitol intravenous infusion	3	14
normosol-M in 5% glucose intravenous infusion	3	14
10% glucose	2	8
5% glucose and 0.02% sodium bicarbonate intravenous infusion	2	8

Solutions of MEROPENEM RANBAXY should not be frozen.

### Incompatibilities

MEROPENEM RANBAXY is compatible with the infusion solutions listed in SPECIAL PRECAUTIONS FOR STORAGE and should not be mixed with or physically added to solutions containing other medicines.

### Medicine Classification

Prescription Medicine

### Package Quantities

White to pale yellow crystalline powder in clear glass vial sealed with grey rubber stopper and flip off seal, containing meropenem 500 mg (equivalent to meropenem trihydrate 570 mg) or 1 g (equivalent to meropenem trihydrate 1.14 g).

Available in packs of 1, 5 and 10 vials.

### Further Information

#### Preclinical Safety Data

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above.

Meropenem is generally well tolerated by the CNS. Effects were seen only at very high doses of 2000 mg/kg and above.

The IV LD50 of meropenem in rodents is greater than 2000 mg/kg. In repeat dose studies of up to 6 months duration only minor effects were seen including a small decrease in red cell parameters and an increase in liver weight in dogs at 500 mg/kg. There was not evidence of mutagenic potential in the 5 tests conducted and no evidence of reproductive toxicity including teratogenic potential in studies at the highest possible level in rats and monkeys. (The no effect dose level of a small reduction in F1 body weight in rats was 120 mg/kg).

There was increased evidence of abortions at 500 mg/kg in a preliminary study in monkeys.

There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies.

The intramuscular formulation caused reversible injection site necrosis.

The sole metabolite of meropenem had a similar low profile of toxicity in animal studies.

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### **Date of Preparation**

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