Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Magnesium Sulfate 20% w/v Solution for Injection or Infusion

magnesium sulfate heptahydrate

PL 56021/0015

Torbay Pharmaceuticals Limited

LAY SUMMARY

Magnesium Sulfate 20% w/v Solution for Injection or Infusion
magnesium sulfate heptahydrate

This is a summary of the Public Assessment Report (PAR) for Magnesium Sulfate 20% w/v Solution for Injection or Infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Magnesium Sulfate Solution for Injection or Infusion in this lay summary for ease of reading.

For practical information about using Magnesium Sulfate Solution for Injection or Infusion, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Magnesium Sulfate Solution for Injection or Infusion and what is it used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK/European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Magnesium Sulfate Solution for Injection or Infusion is used to:
- treat low levels of magnesium in the blood
- prevent and control further seizures (fits) in patients with eclampsia (fits during pregnancy)
- prevent and control seizures (fits) in severe pre-eclampsia (high blood pressure associated with pregnancy).

How does Magnesium Sulfate Solution for Injection or Infusion work?
This medicine is an electrolyte solution and contains the active substance, magnesium sulfate heptahydrate, which plays a number of important roles in the body, including regulation of the nervous and blood systems.

How is Magnesium Sulfate Solution for Injection or Infusion used?
The pharmaceutical form of this medicine is Solution for Injection or Infusion and the route of administration is injection or infusion into a vein.

Due to the high-level of detail in the usage instructions it is best to refer directly to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website, for information on how Magnesium Sulfate Solution for Injection or Infusion is used.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Magnesium Sulfate Solution for Injection or Infusion have been shown in studies?

As the active substance in Magnesium Sulfate Solution for Injection or Infusion has been in clinical use for over 10 years, data were provided in the form of literature references to show that Magnesium Sulfate Solution for Injection or Infusion is safe and efficacious to:

- treat low levels of magnesium in the blood
- prevent and control further seizures (fits) in patients with eclampsia (fits during pregnancy)
- prevent and control seizures (fits) in severe pre-eclampsia (high blood pressure associated with pregnancy).

What are the possible side effects of Magnesium Sulfate Solution for Injection or Infusion?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Magnesium Sulfate Solution for Injection or Infusion approved?

It was concluded that the data provided from literature references had shown that Magnesium Sulfate Solution for Injection or Infusion is effective in conditions detailed above. Furthermore, the well-established use of the active substance Magnesium Sulfate Solution for Injection or Infusion has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Magnesium Sulfate Solution for Injection or Infusion?

A Risk Management Plan (RMP) has been developed to ensure that Magnesium Sulfate Solution for Injection or Infusion is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

The RMP details the important risks of Magnesium Sulfate Solution for Injection or Infusion, how these risks can be minimised, any uncertainties about Magnesium Sulfate Solution for Injection or Infusion (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Magnesium Sulfate Solution for Injection or Infusion:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Use in patients with severe renal failure • Use in patients with hepatic encephalopathy • Use in patients with hepatic failure • Use in patients with heart block
Important potential risks	• Venous irritation and tissue damage in cases of extravasation • Use in patients with impaired renal function • Use in patients with respiratory disease due to the risk of respiratory depression • Potential exacerbation of myasthenia gravis or the precipitation of a myasthenic crisis • Enhancement of non-depolarising muscle relaxants when used with parenteral magnesium • Parenteral administration of magnesium sulfate may enhance the effects of neuromuscular blocking agents or of central nervous system depressants. • Use with calcium channel blockers may lead to calcium ion imbalance and abnormal muscle function • Use with cardiac glycosides • Enhancement of vasodilators when used with magnesium sulfate • Potential for electrolyte imbalance when used with diuretic agents, antacids and laxatives • Potential for respiratory depression of the newborn infant if administered during labour • Potential to cause skeletal adverse effects in the neonate, including hypocalcaemia, skeletal demineralisation and osteopenia, and other skeletal adverse effects with maternal administration of magnesium sulfate for more than 5-7 days.

Summary of safety concerns	
Missing information	• Use during breast feeding

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Magnesium Sulfate Solution for Injection or Infusion
A marketing authorisation for Magnesium Sulfate Solution for Injection or Infusion was granted in the United Kingdom (UK) on 31 May 2023. On 27 October 2023 a change of ownership from Torbay and South Devon NHS Foundation Trust, Torbay Pharmaceuticals (PL 13079/0015) to Torbay Pharmaceuticals Limited (PL 56021/0015) was granted.

The full PAR for Magnesium Sulfate Solution for Injection or Infusion follows this summary.

This summary was last updated in April 2025.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Magnesium Sulfate 20% w/v Solution for Injection or Infusion (PL 13079/0015) could be approved. This product is indicated for the:

- Treatment of magnesium deficiency in hypomagnesaemia.
- Prevention and control of seizures in severe pre-eclampsia.
- Prevention and control of recurrent seizures in eclampsia.

Mechanism of action
Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte. It is a cofactor in numerous enzyme systems and is involved in phosphate transfer, muscle contractility and neuronal transmission.

The precise site of action of magnesium sulfate in eclampsia is not known. Experimentally, magnesium has been shown to block the NMDA subtype of glutamate channel through which calcium enters the cell and cause neuronal damage during cerebral ischaemia. Ischaemia leads to lowering of the transmembrane potential allowing calcium ion influx across the membrane and from the endoplasmic reticulum and mitochondria. This leads to further calcium influx as membrane phospholipids are hydrolysed by activated enzymes. Magnesium blocks calcium at intracellular sites in addition to the outer lipid membrane.

This application was approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 5 December 2019 on grounds relating to quality, safety and efficacy. Following the provision of additional data and information the noted issues were suitably resolved.

A marketing authorisation for Magnesium Sulfate Solution for Injection or Infusion was granted in the United Kingdom (UK) on 31 May 2023. On 27 October 2023 a change of ownership from Torbay and South Devon NHS Foundation Trust, Torbay Pharmaceuticals to Torbay Pharmaceuticals Limited (PL 56021/0015) occurred.

II QUALITY ASPECTS

II.1 Introduction

What Magnesium Sulfate Solution for Injection or Infusion contains

The active substance is magnesium sulfate heptahydrate at a strength of 200 g per litre (approximately 0.8 mmol magnesium per mL). The other ingredients are sulfuric acid and Water for Injections.

The contents of the pack

This medicine is available in 20 mL and 50 mL vials, packed into cartons containing 1 vial or 10 vials. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

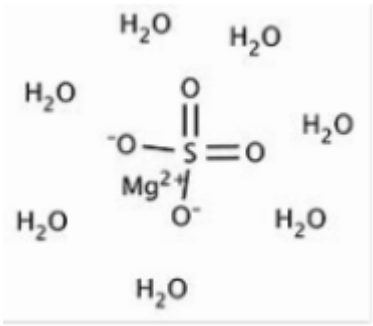
rINN: Magnesium Sulphate Heptahydrate

Chemical Name: As above

Molecular Formula: $MgSO_4,7H_2O$

Molecular Weight: 246.5

Molecular Structure:



Appearance: White or almost white, crystalline powder or brilliant, colourless crystals.

Solubility Freely soluble in water, very soluble in boiling water, practically insoluble in ethanol (96 per cent).

Magnesium Sulphate Heptahydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months without any special storage conditions, is acceptable.

Chemical and physical in-use stability has been demonstrated for 24 hours at a maximum of 25ºC. From a microbiological point of view, the product should be used immediately and the storage of opened vials should be avoided. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology
Magnesium sulfate belongs to the class of inorganic compounds known as alkaline earth metal sulfates. These are inorganic compounds in which the largest oxoanion is sulfate, and in which the heaviest atom not in an oxoanion is an alkaline earth metal.

The scientific literature reports that magnesium sulfate is the second most plentiful cation in the intracellular fluids and is involved in a wide range of activities. It is essential for the activities of many enzymes and it is also important for the role that it plays in neurochemical transmission. The average individual with a bodyweight of 70Kg contains about 2000mEq of magnesium of which 50% is in the bone.

Magnesium salts are well known for their antacid properties but can also be used as laxatives. Magnesium is a depressant of both central nervous and neuromuscular function. It decreases acetylcholine release by motor nerve impulses and reduces the sensitivity of the motor endplate to acetylcholine. Magnesium is also a depressant of cardiac muscle irritability with similar actions to potassium and may act as a physiological calcium blocker. It will block the transient inward current carried by calcium generated by cardiotonic drugs and, because of this action, counteracts ventricular irritability caused by excess digoxin resulting in electronic stabilising of the myocardium.

Research has reported on the effect of oral magnesium supplementation on experimental pre-eclampsia induced by prolonged blockade of nitric oxide synthesis in pregnant rats. The nitric oxide synthesis inhibitor used was N-nitro-L-arginine methyl ester hydrochloride (L-NAME).

Virgin female rats of the Wistar strain (bodyweight 150-200g) were acclimatised in laboratory conditions for at least one week before mating. After mating was confirmed, the rats were divided into treatment groups:-

A Control group rats received saline vehicle (route not stated but inferred oral)
B Rats received L-NAME, 50mg/kg/day ip.
C Rats received L-NAME, 50mg/kg/day ip and magnesium sulfate, 250mg/kg/day oral.
D Rats received L-NAME, 50mg/kg/day ip and magnesium sulfate, 500mg/kg/day oral.
E Rats received L-NAME, 50mg/kg/day ip and magnesium sulfate, 750mg/kg/day oral.

All treatments were started on gestation days 13-14 and continued for 7 days.

Throughout the gestation period the rats were weighed daily and blood pressure (systolic and diastolic) were recorded daily using a tail cuff.

During the gestation period the rats were housed in metabolic cages and daily 24-hour urine was collected for estimation of urinary proteins.

Duration of gestation was noted for each animal and, after delivery, pups were removed, numbered and weighed.

Maternal parameters during pregnancy
Bodyweight was unaffected by treatment. Systolic and diastolic blood pressure was higher than control values in the L-NAME only treated animals and also in those receiving 250mg/kg/day magnesium sulfate. Systolic and diastolic blood pressure was similar to control values in rats receiving 500 or 750mg/kg/day magnesium sulfate.

Foetal effects
Gestation duration was unaffected by treatment. Litter weights were lower in L-NAME only treated rats but were normal in rats receiving magnesium sulfate

Urinary proteins
Twenty-four hour urinary protein levels were higher in rats receiving L-NAME only and in rats receiving 250mg/kg/day magnesium sulfate having significantly raised values compared to controls.

It was concluded that in a chronic nitric oxide deprivation induced model of pre-eclampsia in rats, administration of magnesium sulfate improves the foetal outcome and significantly prevents the development of symptoms of pre-eclampsia like hypertension and proteinuria.

Table 1 Effects of L-NAME (50mg/kg/day) and L-NAME plus magnesium sulfate (250, 500 and 750mg/kg/day) when administrated to pregnant rats. Values are mean ± SE, n-10.

Parameter	Control	L-NAME (50mg/kg/day)	L-NAME plus magnesium sulfate (mg/kg/day)		
			250	500	750
Systolic BP (mmHg)	109 ± 2	142 ± 2***	131 ± 2	94 ± 2	98 ± 3
Diastolic BP (mmHg)	83 ± 3	106 ± 3**	103 ± 3	64 ± 4	73 ± 1
Bodyweight (g)	151 ± 2	157 ± 3	160 ± 1	150 ± 1	143 ± 2
Litter number	9.7 ± 1.5	9.3 ± 2.3	10.0 ± 1	11.0 ± 2	10.0 ± 2
Foetal weight (g)	5.3 ± 0.13	4.1 ± 0.13*	5.9 ± 0.10	6.0 ± 0.20	5.0 ± 0.80
Urinary proteins (mg/l)	8.8 ± 1.2	13.3 ± 0.5**	14.0 ± 0.9**	5.2 ± 1.2	7.7 ± 0.2

P values * <0.05, ** <0.01, *** <0.001

Comment

The pharmacology of magnesium sulfate is well known and although literature to describe its non-clinical characteristics is limited, the available information and data has been adequately described in the non-clinical overview. Given that the extent of clinical use, the findings for secondary pharmacology and safety pharmacology are superseded, although an acceptable discussion is provided.

Secondary pharmacology

Research reported on a 4-week toxicity in dogs. Magnesium sulfate was administered intravenously to female beagle dogs (bodyweight not stated) as a 24-hour intravenous infusion for 4 weeks at dosage levels of 0, 12.5, 50 or 100mg/kg/hr.

The toxic effects are detailed in the toxicology section below.

The ECG results, tabulated below, show that the heart rate, PR, QRS and QT intervals and the QTC values for treated dogs were not significantly different at the end of the 4 week infusion period.

Table 2 ECG in dose during 4 week intravenous infusion of magnesium sulfate (Mean ± SD).

Dose	N	Heart rate (beats/min)		PR interval (m sec)		QRS interval (m sec)		QT interval (m sec)		QTC	
		-1w	4w	-1w	4w	-1w	4w	-1w	4w	-1w	4w

0	3	118 ± 22	122 ± 32	105 ± 13	99 ± 10	50 ± 10	45 ± 4	198 ± 22	189 ± 18	276 ± 9	268 ± 9
12.5	3	122 ± 18	135 ± 14	95 ± 11	94 ± 3	43 ± 2	41 ± 2	194 ± 8	178 ± 12	279 ± 10	267 ± 8
50	3	125 ± 28	97 ± 13	82 ± 10	94 ± 6	43 ± 4	47 ± 6	191 ± 7	205 ± 9	278 ± 36	260 ± 19
100	3	121 ± 20	116 ± 9	85 ± 7	109 ± 4	41 ± 3	53 ± 6	191 ± 10	210 ± 6	271 ± 20	294 ± 18

Dose - mg/kg/hr

Reports provided have evaluated the effect of magnesium and zinc on in vitro and in vivo histamine-induced airway smooth muscle contraction in dogs

In vitro study in guinea pigs
Female guinea pigs (250-400g) were killed with an overdose of ip pentobarbital and sectioning of the aorta. The trachea was removed, dissected from surrounding connective tissues and cut spirally into two tracheal strips. Each strip was mounted in a 10ml organ bath filled with Krebs-bicarbonate buffer aerated with 95% O_2 and 5% CO_2 at 37ºC and prepared for organ bath work using a force displacement transducer to measure relaxation.

Each strip was subjected to a load of 2g for at least 2 hours, with frequent changes of the bath buffer content until baseline tension was stable before study commencement. Zinc sulfate ($ZnSO_4$; 0.1, 0.2, 0.4, 0.8, 1.6, and 3.2mM), magnesium sulfate ($MgSO_4$; 1, 2, 4, and 8mM), or sodium sulfate (Na_2SO_4; 1, 2, 4, and 8mM) was cumulatively added to the organ bath. Relaxation was expressed as a percentage (peak contraction, 0%; full relaxation, 100%). The doses of the cations that reversed histamine-induced contraction by 50% were calculated from the log dose-response curve.

In vivo study in dogs
The relaxant effect of $ZnSO_4$, $MgSO_4$ and Na_2SO_4 was assessed by a direct visualization method with a superfine fibre-optic bronchoscope. Twenty-one mongrel dogs were anaesthetised with iv pentobarbital and paralysed by pancuronium infusion at 0.2mg/kg/hr. The dogs were randomly assigned to three groups: group Zn (n = 7), group Mg (n = 7), and group Na (n = 7). The dogs prepared for table experimentation with the trachea intubated with a special endotracheal tube with a second lumen for insertion of a superfine fibre-optic bronchoscope to monitor the bronchial cross-sectional area (BCA) continuously. The bronchoscope tip was placed at the level between the second and third bronchial bifurcations.

The lungs were mechanically ventilated with a volume-controlled respirator with 100% oxygen and the end-tidal CO_2 maintained at 4.0% to 4.5%. A femoral artery was cannulated to monitor arterial blood pressure and to obtain arterial blood samples. A femoral vein was also cannulated to insert a pulmonary artery catheter. The BCA was measured with NIH Image machine. Bronchoconstriction was elicited with histamine 10µg/kg iv followed by a continuous infusion of 500µg/kg/hr until the end of each experiment. Fluid loading (lactated Ringer's solution, 50mL/kg) and continuous phenylephrine infusion at 0.5 to 2.0µg/kg/min were used to maintain systolic blood pressure > 80mmHg. Thirty minutes after the start of histamine infusion, 1, 10, and 100µM/kg ZnSO4 or 1, 10, 100, and 1000µM/kg MgSO4 or Na_2SO_4 were administered intravenously in groups Zn, Mg, and Na, respectively.

The BCA was assessed before and 30 minutes after the start of histamine infusion and 5 minutes after each dose of $ZnSO_4$, $MgSO_4$, or Na_2SO_4. Changes in BCA were expressed as percentage of the basal area. Arterial blood was also collected simultaneously to measure plasma levels of adrenaline and noradrenaline by gas chromatography-mass spectrometry.

The study protocols were approved by the local university animal care committee.

In vitro study results in guinea pigs
After pre-contraction with histamine, $MgSO_4$ and $ZnSO_4$ relaxed the tracheal strip in a concentration-dependent manner, whereas Na_2SO_4 (except 8mM) did not. The dose of $ZnSO_4$ that reversed histamine-induced contraction by 50% (1.84 ± 0.30mM) was significantly lower than that of $MgSO_4$ (9.38 ± 0.28mM) ($p < .01$).

In vivo study results in dogs
MgSO4 and ZnSO4 dose-dependently increased the percentage of BCA (potency, MgSO4 < ZnSO4), whereas Na2SO4 did not. The plasma concentrations of adrenaline and nor adrenaline were also dose-dependently increased by ZnSO4 and MgSO4 (except 1000μM/kg iv), but not by Na2SO4

The data showed that MgSO4 and ZnSO4 dose-dependently reversed histamine-induced airway smooth muscle contraction in vitro and in vivo. Because Na2SO4 did not produce any effects, the reversal of the contraction may be caused by Mg2+ and Zn2+ but not by sulfate ion.

The authors concluded that because magnesium and zinc produced a spasmolytic effect on the contracted airway, infusion of magnesium and zinc might be effective against asthmatic attack. However, the plasma level of magnesium and zinc should be carefully monitored during the infusion because of their toxicity.

Literature exists on an investigation upon whether systemic magnesium sulfate (acting as an antagonist at the glutamate subtype of N-methyl-D-aspartate receptor) affected inflammatory pain, and whether the nitric oxide pathway was involved.

Adult, male Wistar rats (n = 204), weighing 230-290g were acclimatized for 60 minutes prior to control measurements of paw withdrawal threshold (PWT) to mechanical stimuli.

For the duration of the experiment, the rats were unrestrained in individual clear boxes, raised on a special rack of steel mesh. After control measurements, and a break of 30 minutes, peripheral hyperalgesia was induced by intraplantar injection of 0.1ml of carrageenan (0.5%) into the right hind paw. Hind paw mechanical withdrawal thresholds were assessed by measuring the withdrawal response to von Frey filament stimulation. The von Frey filament was applied to the plantar surface of the tested paw until paw withdrawal occurred, provoking a flexion reflex. An electronic pressure meter automatically recorded the intensity of the stimulus when the paw was withdrawn. Before paw stimulation, the animals had to be quiet, without exploratory or toilet movements and not resting over the paws. Measurements were performed three to five times in each rat, and the average of the middle three values was calculated.

In order to examine whether drugs tested have any effect on the mechanical PWT in rats not treated with carrageenan, the highest doses tested were dissolved in saline and administered in a separate group of rats. Control rats received the corresponding volume of saline. Hind

paw withdrawal threshold to mechanical stimuli was measured at 0, 0.25, 0.5, 1, 2, 3, 4, 5 and 6 hours after intraplantar injection of carrageenan.

The study protocol and animal housing and handling were approved by the local ethical committee

The results showed that magnesium sulfate had no effect when injected locally into the inflamed rat paw. However, subcutaneous magnesium sulfate, at doses of 0.5, 5, 15 and 30mg/kg, reduced the hyperalgesia by 44.4±8.8, 68±8.4, 24.6±6.9 and 45.3±6.7% respectively.

The non-selective nitric oxide synthase inhibitor L-NAME (3 and 5mg/kg, intraperitoneal), significantly reduced the effects of magnesium sulfate. Also, L-arginine (0.4mg/kg, subcutaneously) significantly reversed the effect of L-NAME in the magnesium sulfatetreated rats.

A selective inhibitor of neuronal or inducible nitric oxide synthase, N-ω-Propyl-L-arginine hydrochloride (L-NPA) (0.5, 1 and 2mg/kg, intraperitoneal) and S-methylisothiourea (SMT) (0.005, 0.01 and 0.015mg/kg, intraperitoneal) reduced the effect of magnesium sulfate significantly only at the highest doses tested. When given alone, L-NAME (3 and 5mg/kg) L-NPA (2mg/kg) and SMT (0.015mg/kg) did not have any influence on carrageenaninduced hyperalgesia.

It was concluded that magnesium sulfate was effective against inflammatory pain after systemic, but not after local peripheral administration, and activation of the nitric oxide pathway was probably involved in the anti-hyperalgesic effect of magnesium sulfate. The authors postulated that low doses of systemic magnesium sulfate given as a pre-treatment or a treatment might have a beneficial effect in patients with inflammatory somatic pain.

A report on an in vivo rat study examined the effect of magnesium sulfate on the vascular actions of noradrenaline and angiotensin II.

Female rats of the Wistar strain (200-300g bodyweight) were anaesthetised with intraperitoneal injection of thiobarbital and prepared for table experimentation by cannulation of the trachea, femoral vein (for drug infusion) and artery (for blood pressure recording) and stabilised for 60 minutes

Mean arterial pressure (MAP) was recorded for the whole experimental period. After 15 minutes, an intravenous bolus of either noradrenaline or angiotensin II was given. 15 minutes later intravenous magnesium sulfate was given as a bolus dose and then followed by an infusion for 90 minutes. During the infusion period, an intravenous bolus of either noradrenaline or angiotensin II was given and again, after cessation of the infusion an intravenous bolus of either noradrenaline or angiotensin II was given with a final 15-minute period of blood pressure recording to assess the final control response. Serum magnesium levels were determined before, during and after the magnesium sulfate infusion.

Doses administered were noradrenaline (200ng/kg) angiotensin II (40ng/kg), magnesium sulfate (70mg/kg bolus dose then 35mg/kg/hr). The magnesium doses were chosen to approximate those used in treating pre-eclampsia in humans.

The results showed that noradrenaline resulted in a significant rise in MAP (46±3.7mmHg; p < 0.001). Angiotensin II also resulted in a significant rise in MAP (23±3.6mmHg, p < 0.02). Magnesium sulfate alone had no significant effect on MAP but attenuated the pressor response to both noradrenaline (MAP 16±1.5mmHg) and angiotensin II (MAP, 12±2.5mmHg). After discontinuation of the magnesium sulfate infusion, the control pressor responses to noradrenaline and angiotensin II were again seen (MAP, 39±3.5mmHg and 28±4.2mmHg, respectively).

Predose serum magnesium levels (1.4 ± 0.1mEq/litre) rose significantly during the magnesium sulfate infusion period (4.9 ± 0.2mEq/litre [p<0.001]) and returned to baseline (1.5 ± 0.1mEq/litre) after discontinuation after the infusion stopped (p<0.001]).

It was concluded that, although magnesium sulfate is not a primary antihypertensive agent, it might have effects on blood pressure by attenuating the actions of circulating vasoconstrictors.

A paper on the effect of magnesium sulfate administration on blood-brain barrier in a rat model of intraperitoneal sepsis. They noted that permeability changes in the blood-brain barrier (BBB) and their possible contribution to brain oedema formation have a crucial role in the pathophysiology of septic encephalopathy. Magnesium sulfate has been shown to have a protective effect on BBB integrity in multiple experimental models. They therefore wished to determine whether magnesium sulfate administration could have any protective effects on BBB derangement in a rat model of sepsis.

A randomised controlled experimental study was performed on adult male rats of the Sprague Dawley strain (bodyweight not stated) with intraperitoneal sepsis induced by using the infected fibrin-thrombin clot model. To examine the effect of magnesium in septic and sham-operated rats, a dose of 750μm/kg magnesium sulfate was given intramuscularly immediately after surgery. Control groups for both infected and shamoperated rats were injected with equal volume of saline. Those rats surviving for 24 hours were killed and the brains removed for the investigation of brain tissue specific gravity and BBB integrity by the spectrophotometric assay of Evans blue dye extravasations. Another set of experiments was performed for haemodynamic measurements and plasma magnesium level analysis. Rats were allocated into four parallel groups undergoing identical procedures.

The study protocol and animal housing and handling were approved by the local ethical committee.

The results showed that sepsis significantly increased BBB permeability to Evans blue. The dye content of each hemisphere was significantly lower in the magnesium-treated septic rats than in control septic animals. In septic animals treated with magnesium sulfate, specific gravity was higher than in the untreated septic animals, indicating less oedema formation with the administration of magnesium. A significant decrease in plasma magnesium levels was observed 24 hours after the induction of sepsis. The dose of magnesium that was used maintained the baseline plasma magnesium levels in magnesium-treated septic rats.

It was concluded that magnesium administration attenuated the increased BBB permeability defect and caused a reduction in brain oedema formation in this rat model of intraperitoneal sepsis.

Table 3 Plasma magnesium concentrations (means ± SD.)

Measurement	Group (n=8)	Basal	24 hours	Two-tailed P values
Plasma Mg (mM)	C S C-Mg S-Mg	1.11 ± 0.05 1.09 ± 0.05 1.10 ± 0.06 1.13 ± 0.03	1.10 ± 0.05 0.89 ± 0.06[a],[b] 1.29 ± 0.06 1.01 ± 0.08[c]	NS 0.0078 0.0078 0.0156
Kruskal–Wallis test statistic		2.708	26.863	
degrees of freedom		3	3	
P		>0.05	<0.0001	

NS, not significant;
C - sham control (C),
C - Mg sham - control $MgSO_4$-treated
S - septic
S - Mg septic - $MgSO_4$-treated Dunn's multiple comparisons test: a septic v sham control, $P < 0.05$;
b septic v sham control $MgSO_4$-treated, $P < 0.001$;
c septic $MgSO_4$-treated v sham control $MgSO_4$-treated, $P < 0.01$.
Paired serum magnesium levels compared within groups using a Wilcoxon signed rank test.

Table 4 Assessment of blood–brain barrier permeability by Evans blue dye content in brain tissue (means ± SD).

Measurement	Group (n=8)	Left hemisphere	Right hemisphere	Two-tailed P values
Evans blue dye (μg/g)	C S C-Mg S-Mg	0.00160 ± 0.0003 0.00466 ± 0.0002[a],[b] 0.00135 ± 0.0002 0.00218 ± 0.0005	0.00145 ± 0.0003 0.00641 ± 0.0003[c],[d] 0.00145 ± 0.0003 0.00199 ± 0.0007	0.33 0.13 0.44 0.57
Kruskal–Wallis test statistic		19.720	23.039	
degrees of freedom		3	3	
P		< 0.001	< 0.0001	

Dunn's multiple comparisons test:
C - sham control (C),
C - Mg sham - control $MgSO_4$-treated
S - septic
S - Mg septic - $MgSO_4$-treated
a - septic versus sham control, $P < 0.01$;
b - septic versus sham control $MgSO_4$-treated, $P < 0.001$;
c - septic versus sham control, $P < 0.001$;
d - septic versus sham control $MgSO_4$-treated, $P < 0.001$.
A Mann–Whitney test was used for within-group comparisons.

Table 5 Assessment of oedema by specific gravity of brain tissue

Measurement	Group (n=8)	Left hemisphere	Right hemisphere	Two-tailed P values
SG	C S C-Mg S-Mg	1.0444 ± 0.0001 1.0429 ± 0.0009[a],[b] 1.0444 ± 0.0002 1.0438 ± 0.0007	1.0443 ± 0.0002 1.0424 ± 0.0012[c],[d] 1.0444 ± 0.0001 1.0439 ± 0.0004[e]	0.24 0.44 0.44 0.24
Kruskal–Wallis test statistic		18.831	24.724	
degrees of freedom.		3	3	
P		< 0.001	<0.0001	

Dunn's multiple comparisons test:
C - sham control (C),
C - Mg sham - control $MgSO_4$-treated
S - septic
S - Mg septic - $MgSO_4$-treated
a - septic versus sham control, P < 0.001;
b - septic versus sham control $MgSO_4$-treated, P < 0.01;
c - septic versus sham control, P < 0.01;
d - septic versus sham control $MgSO_4$-treated, P < 0.001;
e - septic $MgSO_4$-treated versus sham control $MgSO_4$-treated, P < 0.05.
Mann–Whitney test used for within-group comparisons.

III.3 Pharmacokinetics

From the literature, it is considered that magnesium sulfate is absorbed following oral administration. It is widely distributed with 50% found in bone, 45% as an intracellular ion and 5% in extracellular fluid. About 30% of magnesium in the skeleton represents an exchangeable pool. Magnesium concentration in intracellular fluid and plasma is about 15 and 0.75mM/l respectively and the major excretory pathway is renal with both oral and intravenous loads rapidly eliminated. It is also reported that renal impairment may cause magnesium accumulation.

Pharmacokinetic studies conducted in experimental animals, as commonly conducted on organic drugs, could not be found for magnesium sulfate. Pharmacokinetic studies in man have been published and were submitted.

The reports of some toxicity studies did include blood sampling to provide plasma levels. For this marketing authorisation application, absorption of magnesium sulfate is not an issue because the product is administered intravenously..

A report on a 4-week toxicity in dogs was provided.

Magnesium sulfate was administered intravenously to female beagle dogs (bodyweight not stated) as a 24-hour intravenous infusion at dosage levels of 0, 12.5, 50 or 100mg/kg/hr.

The magnesium plasma levels, tabulated below, show that there is a dose-related increase in plasma magnesium levels increasing over the first 24-hour infusion period. After cessation of infusion on day 29, all values return to normal within 24 hours.

Table 6 Concentration of magnesium in plasma in dogs during a 4-week intravenous infusion of magnesium sulfate.

Dose (mg/kg/hr)	Time after start of infusion on day 1 (mg/dl)					Day 14	Time after stop of infusion on day 29 (mg/dl)			
	0	1hr	4hr	8hr	24hr		BS	1hr	4hr	24hr
12.5	2.1 ± 0.2	2.5 ± 0.2	2.7 ± 0.2	2.8 ± 0.1	2.9 ± 0.1	2.9 ± 0.2	2.7 ± 0.1	2.4 ± 0.1	1.9 ± 0.1	2.0 ± 0.2
50	2.0 ± 0.1	3.4 ± 0.2	4.2 ± 0.1	4.4 ± 0.2	4.7 ± 0.3	5.7 ± 0.6	5.1 ± 0.2	4.5 ± 0.1	3.2 ± 0.3	2.4 ± 0.4
100	2.0 ± 0.2	4.4 ± 0.3	6.5 ± 0.4	6.7 ± 0.4	7.5 ± 0.4	8.7 ± 0.7	7.6 ± 0.2	6.8 ± 0.5	4.3 ± 0.9	2.8 ± 0.6

A report on a 2-week toxicity in dogs was provided.

Magnesium sulfate was administered intravenously to female beagle dogs (bodyweight not stated) as a 24-hour intravenous infusion at dosage levels of 0, 12.5, 50, 100 or 200mg/kg/hr.

The magnesium plasma levels, tabulated below, show that there is a dose-related increase in plasma magnesium levels increasing over the first 24-hour infusion period. After cessation of infusion on day 15, all values return to normal within 24 hours.

Table 7 Concentration of magnesium in plasma in dogs during a 2-week intravenous infusion of magnesium sulfate.

Dose (mg/kg/hr)	ID	Time after start of infusion on day 1 (mg/dl)								Time after stop of infusion on day 15 (mg/dl)					
		0	15m	30m	1h	2h	4h	8h	24h	BS	1h	2h	4h	8h	24h
12.5	2101	1.8	2.1	2.1	2.1	2.5	2.7	2.8	2.8	2.8	2.4	2.1	2.1	2.2	1.7
	2102	1.9	1.9	1.9	2.2	2.3	2.3	2.5	2.6	2.6	2.0	1.9	2.2	2.2	1.9
50	3101	1.9	2.2	2.6	3.1	3.7	4.0	4.8	4.6	5.4	4.5	3.8	3.3	3.4	2.1
	3102	2.1	2.5	2.6	3.2	3.9	4.3	4.8	4.7	4.7	3.8	3.2	2.9	3.2	2.1
100	4101	1.9	2.7	3.2	4.2	5.0	5.8	6.8	6.6	7.4	5.8	4.4	3.5	3.4	2.0
	4102	1.9	2.9	3.2	4.2	5.0	6.8	6.4	7.0	7.4	6.4	4.6	4.0	3.6	2.2
200	5101	1.8	3.2	4.2	5.8	8.2	9.0	7.8	11.7	Died or sacrificed in a moribund state on day 2					
	5102	1.6	3.4	4.7	6.0	8.4	9.6	10.5	12.9						

A publication reported that, following the administration of 5.5mg/kg lithium or 160mg/kg magnesium sulfate, the maternal blood, foetal blood, amniotic fluid and chorionic fluid of pregnant mongrel dogs were analysed for the presence of these substances. When maternal blood levels of lithium were maintained at 0.45±0.15mEq/l for 2 hours, lithium did not appear in the foetal blood, amniotic fluid, or chorionic fluid. When the maternal blood level

of lithium approached 3.0mEq/l in one animal, traces of lithium appeared in the foetal blood but not in the amniotic or chorionic fluid.

Maintaining the maternal blood level of magnesium at 6.1±4mg% for 2 hours was not sufficient to produce a significant increase in the level of magnesium in the foetal blood, amniotic fluid, or chorionic fluid.

The study conclusion was that moderately elevated maternal blood levels of lithium or magnesium did not produce rapid transfer of these substances to the foetal circulation.

A report was provided on serum magnesium levels in a pharmacology table study in rats (methods detailed in section 2.4.2, above). Predose serum magnesium levels (1.4±0.1mEq/litre) rose significantly during the magnesium sulfate infusion 35mg/kg/hr period (4.9±0.2mEq/litre [$p<0.001$]) and returned to baseline (1.5±0.1mEq/litre) after discontinuation after the infusion stopped ($p<0.001$]).

Comment
The non-clinical pharmacokinetics of magnesium sulfate is limited in published literature and the discussion in the non-clinical is brief with some focus upon the clinical characteristics. This approach can be considered to be acceptable given the nature of magnesium sulfate and given the well-established use of magnesium in clinical practice.

III.4 Toxicology

Single dose toxicology

The following LD_{50} values (mg/kg bodyweight) are reported in the literature.

Table 8 LD_{50} values in a range of animals by iv, ip or sc routes

Species	Route		
	IV	IP	SC
Mouse	1,100		
Rat	1,100		
Guinea Pig	1,100		1,800*
Rabbit	1,100		1,750*
Cat	1,100		1,000*
Dog	750	1,600	1,750
Monkey	1,100		

* Minimum lethal Dose

A report on a single dose toxicity study of magnesium sulfate in rats and dogs was provided.

Rat
Magnesium sulfate was administered intravenously to male and female rats of the Sprague Dawley Strain (6 weeks of age) at a single dose of 90, 130, 200, 300 or 450mg/kg and observed for any signs of toxicity for up to 14 days post dose.

The results showed that deaths occurred in the 200mg/kg group and above in both sexes. The calculated LD_{50} values were 206mg/kg (male) and 174mg/kg (female).

In the surviving animals in the 130mg/kg and higher dosage groups tonic convulsions, abnormal gait and tachypnoea was seen immediately post dose returning to normal by 15 minutes post dose.

There were no treatment-related changes to the bodyweight or gross pathology.

Dog
Magnesium sulfate was administered intravenously to female beagle dogs (bodyweight not stated) as an infusion for 6 hours of 75, 300 or 1,200mg/kg (rate of 12.5, 50 or 200mg/kg/hr respectively) and observed for any signs of toxicity.

The results showed that no deaths occurred in any of the treatment groups and it was considered that the lethal dose level was higher than 1,200mg/kg (200mg/kg/hr)

In the 1,200mg/kg dose group, vomiting, decreased spontaneous movement, staggering gait, prone position and flush of the conjunctiva and ear auricles were seen immediately post dose returning to normal by 1 hour post dose.

There were no treatment-related changes to the bodyweight, food consumption or gross pathology.

Repeat dose toxicology
A report on 2-week toxicity in dogs was provided.

Magnesium sulfate was administered intravenously to female beagle dogs (bodyweight not stated) as a 24-hour intravenous infusion at dosage levels of 0, 12.5, 50, 100 or 200mg/kg/hr. A 2-week follow-up observation period after completion of the dosing period of 2 weeks was conducted using 2 control dogs and 2 dogs from the 100mg/kg/hr dose group.

One of 2 dogs in the 200mg/kg/hr dose group died 32 hours after the start of the infusion and, at the same time, the remaining animal was killed because of its moribund state.

Treatment related changes were listed as decreased food consumption, bodyweight gain, anaemia, mild prolongation of conduction time in ECG and tubular basophilia in the kidneys of dogs receiving 100mg/kg/hr. Slightly decreased calcium levels were recorded in animals receiving 50mg/kg/hr with larger decreases noted at higher dose levels.

During the recovery period the treatment related changes disappeared and reversibility was suggested.

Because the change in calcium levels was slight at 50mg/kg/hr the authors concluded that the non-toxic dose level of magnesium sulfate was 50mg/kg/hour under the conditions of the study.

Table 9 ECG in dose during 2-week intravenous infusion of magnesium sulfate with 2-week recovery observations

Dose	Dog No	PR interval (m sec)			QRS interval (m sec)			QT interval (m sec)			QTC		
		-2w	2w3	R2w	-2w	2w3	R2w	-2w	2w3	R2w	-2w	2w3	R2w
0	1101	88	86		43	41		193	175		243	233	
	1102	75	71		38	40		190	191		266	261	
	1103*	86	88	86	41	38	38	166	166	178	240	263	270
	1104*	95	83	100	43	46	40	193	181	186	288	278	270
12.5	2101	80	93		41	46		180	200		253	251	
	2102	98	81		48	36		216	201		260	258	
50	3101	100	101		45	41		168	191		246	276	
	3102	88	98		41	43		195	196		263	251	
100	4101	81	93		43	41		183	205		268	276	
	4102	83	108		58	51		185	213		253	286	
	4103*	nd	106	80	50	61	51	196	241	201	258	298	291
	4104*	90	111	88	40	46	36	166	nd	185	255	nd	293
200	5101**	85	(136)		43	(71)		193	(315)		275	(408)	
	5102**	91	(131)		40	(95)		158	(325)		263	(390)	

Dose - mg/kg/hr
* Recovery groups
** Died or killed in moribund state on day 2 (moribund values in brackets)

Table 10 Changes in blood calcium levels during 2-week intravenous infusion of magnesium sulfate with 2-week recovery observations

Dose	Dog No	Blood Calcium (mEq/l)		
		-2w	2w3	R2w
0	1101	10.6	9.5	
	1102	10.9	9.9	
	1103*	10.9	11.1	11.0
	1104*	10.3	10.4	10.5
12.5	2101	10.5	9.8	
	2102	10.7	9.8	
50	3101	10.9	8.9	
	3102	11.1	8.8	
100	4101	11.0	9.9	
	4102	11.1	10.4	
	4103*	10.5	8.8	10.8
	4104*	11.2	6.7	11.3
200	5101**	10.8	(7.4)	
	5102**	10.8	(7.0)	

Dose - mg/kg/hr
* Recovery groups
** Died or killed in moribund state on day 2 (moribund values in brackets).

A report on a 4 week toxicity in dogs was provided.

Magnesium sulfate was administered intravenously to female beagle dogs (bodyweight not stated) as a 24-hour intravenous infusion at dosage levels of 0, 12.5, 50 or 100mg/kg/hr.

No deaths occurred during the study.

Treatment related changes were listed as decreased food consumption, bodyweight gain, anaemia, increased urine volume, decreased serum calcium, increased inorganic phosphorus levels, slight prolongation of conduction time in ECG and tubular basophilia in the kidneys of dogs receiving 100mg/kg/hr. Slightly decreased calcium levels were recorded in animals receiving 50mg/kg/hr with larger decreases noted at higher dose levels.

The ECG results are described in the Safety Pharmacology section above (2.4.2)

Because the change in calcium levels was slight at 50mg/kg/hr the authors concluded that the non-toxic dose level of magnesium sulfate was 50mg/kg/hr under the conditions of the study.

Table 11 Changes in blood calcium and phosphorus levels during 4-week intravenous infusion of magnesium sulfate (Mean ± SD, 3 dogs/group.

Test item (units)	Period	Dose (mg/kg/hr)			
		0	12.5	50	100
Calcium Mg/dl	-2w	10.4 ± 0.2	10.3 ± 0.1	10.4 ± 0.1	10.7 ± 0.3
	-1w	10.5 ± 0.2	10.1 ± 0.2	10.4 ± 0.1	10.2 ± 0.1
	2w	10.4 ± 0.3	10.2 ± 0.3	9.1 ± 0.2	7.8 ± 1.3*
	4w	10.1 ± 0.5	9.5 ± 0.5	9.1 ± 0.2	7.9 ± 1.1**
Phosphorus (mg/dl)	-2w	6.7 ± 0.6	6.8 ± 0.6	7.2 ± 0.3	7.4 ± 0.5
	-1w	6.3 ± 0.12	6.4 ± 0.5	7.0 ± 0.9	6.4 ± 0.3
	2w	6.2 ± 0.4	6.8 ± 0.4	8.2 ± 0.8**	9.0 ± 0.7**
	4w	5.7 ± 0.6	5.7 ± 0.8	6.7 ± 0.8	8.0 ± 1.0*

* $p < 0.05$ significantly different from control value.
** $p < 0.01$ significantly different from control value.

Genotoxicity
Two studies have assessed the mutagenicity of magnesium sulfate, a reverse mutation test with bacteria and a chromosomal aberration test with mammalian cells in culture.

Reverse mutation test
The study was conducted in bacteria, *Salmonella typhimurium* TA100, TA98, TA1535 and TA1537 and *Escherichia coli* WP2 uvrA. Following a dose range finding study the maximum dose level was set at 5000µg/plate with or without the presence of S9.

The results from the dose range finding and main studies showed that magnesium sulfate did not increase the number of colonies with reverse mutation in any of the strains with or without the presence of S9. The positive controls confirmed the study's ability to detect the mutation changes.

Table 12 Reverse mutation test of magnesium sulfate (main study)

± S9	Test substance conc (µg/plate)	Number of reventant (No of colonies/plate)				
		Base-pair substitution type			Frameshift type	
		TA100	TA1535	WP2 *uvrA*	TA98	TA1537
-S9	Solvent control	140 146 (143)	8 12 (10)	25 24 (25)	21 29 (25)	9 12 (11)
	156				21 20 (21)	
	313	133 134 (134)	12 14 (13)	23 21 (22)	17 15 (16)	10 8 (9)
	625	144 150 (147)	14 15 (15)	24 20 (22)	19 16 (18)	16 7 (12)
	1250	128 153 (141	12 12 (12)	21 24 (23)	18 21 (20)	7 10 (9)
	2500	142 145 (144)	13 15 (14)	22 20 (21)	16 16 (16)	8 8 (8)
	5000	144 129 (137	11 7 (9)	24 20 (22)	15* 21* (18)	12 6 (9)
+S9	Solvent control	154 135 (145)	15 18 (17)	31 26 (29)	36 41 (39)	12 14(13)
	156					14 12 (13)
	313	145 135 (141)	9 13 (11)	23 28(26)	39 30 (35)	14 15 (15)
	625	160 147 (154)	10 9 (10)	30 21 (26)	26 38 (32)	18 15 (17)
	1250	145 163 (154)	6 7 (7)	22 22 (22)	32 32 (32)	12 10 (11)
	2500	146 141 (144)	11 9 (10)	21 31 (26)	35 31 (33)	14 10 (12)
	5000	137 152 (145)	11 10 (10)	21 18 (20)	35 31 (33)	13* 9* (11)
Positive	Name	AF-2	NaN_3	AF-2	AF-2	ICR-191
control, S9 not required	conc (µg/plate)	0.01	0.5	0.01	0.1	1.0
	No colonies/plate	815 869 (827)	431 361 (396)	132 142 (137)	437 403 (420)	2024 1827 (1926)

Positive control, S9 required	Name	B[a]P	2AA	AF-2	B[a]P	B[a]P
	conc (μg/plate)	5.0	2.0	10.0	5.0	5.0
	No colonies/plate	804 866 (835)	202 232 (217)	433 453 (443)	195 204 (200)	81 72 (77)

AF-2	2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
NaN_3	Sodium azide
ICR-191	2-Methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine 2HCl
B[a]P	Benzo[a]pyrene
2AA	2-Aminoanthracene
*	Growth inhibition of test bacterium observed
( )	Average number of colonies at each concentration

Chromosomal aberration study

This study, conducted with mammalian cells, a Chinese hamster lung fibroblast cell line (CHL) in culture was used and the maximum dose was set at 5.0mg/ml in both the direct and metabolic activation methods.

The results showed that magnesium sulfate did not induct any increase in the incidence of cells with chromosomal aberration or those with gnome mutation (polyploidy) in any of the strains with or without metabolic activation.

The authors concluded that magnesium sulfate does not have mutagenic potential under the presence of experimental conditions.

Table 13 Chromosomal aberration test of magnesium sulfate with CHL cells in culture (direct method) [200 cells observed]

S9	Time (h)	Conc (mg/ml)	Polyploidy cells (%)	Judge	Type of aberration (%)								Judge
					g	ctb	cte	csb	cse	others	TA	TAG	
	24-0	N.T	1.5	-	0.0	0.5	0.0	0.0	0.0	0.0	0.5	0.5	-
		S.C	1.5	-	1.0	0.5	0.5	0.0	0.0	0.0	1.0	2.0	-
		1.25	0.5	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		2.5	0.5	-	0.0	1.0	0.0	0.0	0.0	0.0	1.0	1.0	-
		5.0	0.5	-	0.0	1.0	0.0	0.0	0.0	0.0	1.0	1.0	-
		P.C.	0.0	-	2.5	25.5	30.5	0.0	2.5	0.0	47.0	49.0	+
	48-0	N.T	0.0	-	0.0	0.0	0.5	0.0	0.0	0.0	0.5	0.5	-
		S.C	0.5	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		1.25	0.5	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		2.5	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		5.0	1.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		P.C.	0.0	-	1.0	16.0	49.5	0.5	5.0	0.0	58.5	59.5	+

Time: exposure time - recovery time
NT - not treated
SC : Solvent control (saline)

PC - Positive control (Mitomycin C 0.005μ/ml)
g - chromatid gap and chromosome gap
ctb - chromatid break
cte – chromatid exchange
csb - chromosome break
cse - chromosome exchange others - fragmentation etc.
TA - Total aberrant cells excluding gap
TAG - Total aberrant cells including gap

Table 14 Chromosomal aberration test of magnesium sulfate with CHL cells in culture (metabolic activation method) [200 cells observed]

S9	Time (h)	Conc (mg/ml)	Polyploidy cells (%)	Judge	Type of aberration (%)								Judge
					g	ctb	cte	csb	cse	others	TA	TAG	
	6-18	N.T	0.0	-	0.0	0.5	0.0	0.0	0.0	0.0	0.5	0.5	-
		S.C	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		1.25	2.0	-	0.0	0.5	0.0	0.0	0.0	0.0	0.5	0.5	-
		2.5	0.5	-	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.5	-
		5.0	1.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		P.C.	1.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
	6-18	N.T	0.5	-	0.0	0.5	0.5	0.0	0.0	0.0	0.5	0.5	-
		S.C	0.5	-	0.0	0.5	1.0	0.0	0.0	0.0	1.0	1.0	-
		1.25	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		2.5	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		5.0	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
		P.C.	0.0	-	4.5	38.5	69.5	0.0	4.5	0.0	84.5	84.5	+

Time: exposure time - recovery time
NT - not treated
SC - Solvent control (saline)
PC - Positive control (N-Nitrosodimethylamine 0.4mg/ml)
g - chromatid gap and chromosome gap
ctb - chromatid break cte - chromatid exchange
csb - chromosome break
cse - chromosome exchange others – fragmentation etc.
TA - Total aberrant cells excluding gap
TAG - Total aberrant cells including gap

Carcinogenicity studies

It has been reported in the literature that magnesium compounds have not been shown to have any carcinogenic activity.

No published papers could be found on the carcinogenicity of magnesium sulfate.

Reproductive and developmental toxicology

A report on a peri and post natal study in the rat with magnesium sulfate administered subcutaneously was provided.

Magnesium sulfate, at dose levels of 250, 500 and 1000 mg/kg, was administered subcutaneously three times daily to female rats of the Sprague Dawley strain from day 15 through day 20 of gestation. The effects of the compound on dams and F_1 animals were examined.

The results showed that, in the dams, decreased food consumption was observed in the 500 and 1000mg/kg groups with hypolocomotion, pronation, bradypnoea and decreased body weight gain were observed in the 1000mg/kg group. There were no effects on the delivery or lactation conditions and necropsy from administration of magnesium sulfate.

In the F_1 animals, low body weight, delays in differentiation (eruption of lower incisor, opening of eyelid) and reversible change in ribs (wavy rib) were observed in the 1000mg/kg group, but there were no effects from administration of magnesium sulfate in viability, functional examinations, behaviour tests or reproductive ability.

Based on the above results, under the conditions of this study, the authors concluded that the non-toxic dose levels of magnesium sulfate for general toxicological effects on dams was 3 x 250 mg/kg/day, for reproductive ability of dams was 3 x 1000 mg/kg/day and for development of F_1 animals was 3 x 500 mg/kg/day.

Table 15 Delivery data and macropathological findings of F_0 dams

Dose (mg/kg)		0	250	500	1000
No pregnant females		19	19	20	19
No of females with live pups		19	19	20	20
Delivery index (%) [a]		100	100	100	100
Gestation period (days) Mean ± SD		22.4 ± 0.4	22.1 ± 0.4*	22.2 ± 0.3	22.4 ± 0.3
No of implantations	Total	329	327	337	340
	Mean ± SD	17.3 ± 2.3	17.2 ± 1.9	16.9 ± 2.6	17.0 ± 2.1
No of still born (%)		9 (3.2)	3 (1.0)	12. (3.5)	12 (3.5)
No of live born	Total	288	297	302	308
	Mean ± SD	15.2 ± 2.5	15.6 ± 2.2	15.1 ± 2.6	15.4 ± 2.0
Life birth index (%) [b]		87.7	90.8	90.2	90.8
No of dames with abnormal findings [c]		0/23	0/23	0/22	0/16

a (No of females which delivered live pups/No pregnant females) x 100
b (No of live born pups/No of implantations) x 100 c No of dams necropsied on day 21 after delivery
* - Significant difference from control ($P<0.05$)

Table 16 Reproductive ability of F_1 animals

Dose (mg/kg)	0	250	500	1000
No of pairs examined (male/female)	19/19	19/19	20/20	20/20
No of pairs copulated	18	19	19	20
Copulation index (%) [a]	94.7	100.0	95.0	100.0
Day until copulation period (Mean ± SD)	2.9 ± 1.3	3.5 ± 2.8	2.8 ± 1.3	3.0 ± 1.6
No of females pregnant	18	18	18	17
Fertility index (%) [b]	100.0	94.7	94.7	85.0

Caesarean section data on F_1 dams					
No of corpora lutea	Total	338	310	318	293
	Mean ± SD	18.8 ± 2.8	17.2 ± 3.0	17.7 ± 3.0	17.2 ± 2.6
No of implantations	Total	306	291	297	276
	Mean ± SD	17.0 ± 2.1	16.2 ± 4.2	16.5 ± 3.2	16.2 ± 3.9
Implantation index (%) [c]		91.0	92.7*	93.5	93.1
Post implantation loss [d]	Total	17	22	17	20
	%	5.1	7.3	5.6	7.1
No of live embryos	Total	289	269	280	256
	Mean ± SD	16.1 ± 1.5	14.9 ± 4.1	15.6 ± 3.3	15.1 ± 3.8

a - (No of animals copulated/No of animals mated) x 100
b - (No of pregnant females/ No of females copulated) x 100
c - (No of implantations/ No of corpora lutea) x 100
d - Resorbed embryo, placental remnant, macerated foetus and dead foetus
* - Significant difference from control ($P<0.05$)

Researchers investigated the effects of magnesium exposure on the neonatal mouse brain at different postnatal ages to determine whether magnesium sulfate treatment causes significant cell death in the developing mouse brain.

C57Bl/6 infant mice were treated with four doses of magnesium sulfate (250 mg/kg) on postnatal days 3 (P3), 7 (P7) or 14 (P14). To control for litter variability, a litter matching approach was used with control and experimental pups taken from the same litters, so that each experimental condition had its own group of littermate controls.

From prior studies it was known that peak sensitivity to drug-induced developmental neuroapoptosis occurred in the postnatal day 3 (P3) to P7 period, but some neuronal groups remain sensitive until at least P14. Therefore magnesium sulfate or saline was administered to infant mice at P3, P7, or P14 and evaluated the brains 8–24 hours later by histological methods that allowed detection and quantification of apoptotic neurons. As sometimes magnesium sulfate is administered to human obstetrics patients in doses that may exceed 50g in a 24-hour period, (c1g/kg) magnesium sulfate was administered by intraperitoneal injection to infant mice at a dose of 250mg/kg at time zero and at 1, 2 and 3 hours, for a total dose of 1g/kg. Pups were excluded from the study if they appeared malnourished or, if at the beginning of the experiment, their stomach was not full of milk (as visualised through the relatively transparent abdominal wall).

In addition to histological studies, separate groups of animals were used to monitor magnesium blood levels on P7 and P14 following administration of magnesium sulfate by the above-described dosing regimen.

Separate groups of 16 pups (n = 8), randomly chosen from at least 4 litters, were treated with magnesium sulfate or saline for histological evaluation of neuroapoptosis at ages P3, P7, and P14. At 8 hours post-treatment, the animals were anaesthetized, perfused with fixative and their brains cut into serial sagittal vibratome sections (70μm). Every 6th sagittal section was chosen for evaluation using unbiased, systematic random sampling according to stereological principles. This permitted sampling 6 to 10 sections from half of each brain depending on the area of interest and age.

These sections were processed histologically, including Caspase-3 immunohistochemistry, cupric silver staining, with electron microscopy techniques used to examine the treated brains for neurotoxic effects.

The results showed that magnesium sulfate -treated animals demonstrated evidence of drug effect approximately 5-10 minutes after the initial dose. Although tone was difficult to assess, spontaneous movement in the treated animals was decreased compared to controls. Righting reflex remained intact but sluggish and all animals showed a robust response to tail pinch. The drug-induced effects lessened by approximately 45-50 minutes and the effects did not seem to be additive with subsequent dosing. Treated animals showed no evidence of cardiorespiratory impairment compared to saline controls with observation of the pups conducted every 30 minutes during the study. It was noted at all observation points that their skin was pink with no discolouration and there were no signs of any respiratory difficulty. The animals remained with their mother throughout the experiment and it was also noted that they were able to nurse without difficulty, and that their stomachs contained milk for the duration of the experiment. At the time of sacrifice (8 hours), no differences in behaviour were identified between the control and treated animals.

Qualitative evaluation using cupric silver staining revealed widespread damage throughout the brain in P7 animals. Results of electron microscopy confirmed that the cell death process was apoptotic in nature. Quantitative evaluation of damage to the cortex, caudateputamen, hippocampus, thalamus, and cerebellum showed that magnesium treatment caused significant brain damage in animals treated on P3 and P7, but not P14.

It was concluded that administration of high doses of magnesium may be detrimental to the foetal brain, particularly if exposure occurs during critical periods of neurodevelopment. Therefore, very high doses of magnesium (50g or more, which for a small woman would be 1g/kg) may be associated with increased mortality and gross CNS injury, whereas at substantially lower doses, magnesium may be associated with a slight improvement in acute neurological outcome.

A report on the intravenous infusion of magnesium sulfate and regional redistribution of foetal blood flow during maternal haemorrhage in late-gestation gravid ewes was provided.

The authors noted that although magnesium sulfate is commonly prescribed for women with pre-eclampsia as prophylaxis against seizure and for women with preterm labour as a tocolytic agent there was limited information (at the time of publication 1999) on its effects on the foetus. It is of particular concern that women with pre-eclampsia or in premature labour are at high risk for abruptio placentae with consequent compromise of foetal oxygenation. Magnesium sulfate is a vasodilator and thus may exert cardiovascular effects on the foetus. The goal of this study was to evaluate the effects of magnesium sulfate on foetal organ blood flow, especially regional cerebral blood flow, during the stressful condition of maternal haemorrhage.

Studies were performed with 11 long-term instrumented pregnant ewes and their foetuses at 121 to 128 days' gestation (term, 147 days gestation). Animals were randomly allocated to either the experimental (n = 5) or the control (n = 6) group. After a 60-minute baseline period, experimental foetuses received intravenous magnesium sulfate diluted in 0.9% sodium chloride (0.3g loading dose, then 0.3g/h at a rate of 3mL/h) and control foetuses were infused with an equivalent volume of intravenous 0.9% sodium chloride. After 60 minutes of this infusion-only period, the infusions were continued and ewes were intermittently bled 4

times at a rate of 5mL/kg for 10 minutes with 5 minutes between haemorrhages. The total blood lost at the end of the haemorrhage-plus-infusion hour was 20mL/kg. The infusions were continued and the sheep were observed for 1 hour after this period (post-haemorrhage period). At the end of baseline, infusion-only, and haemorrhageplus-infusion periods, foetal and maternal blood pressures and blood gas values were measured and foetal organ blood flows were determined through a fluorescent microsphere technique. Repeated-measures analysis of variance and Wilcoxon tests were used to determine the significance of changes in haemodynamic, blood gas and organ blood flow parameters between different time points within each group. Comparisons between groups were made with rank sum tests (Mann-Whitney tests).

The results showed that there were no significant differences between groups or within groups for baseline and infusion-only measurements in any measured haemodynamic or haematologic factor. Mean maternal blood pressure decreased significantly ($P < 0.05$) after haemorrhage, with similar median decrements in both control and experimental groups of 41mmHg (interquartile range, 24-57mmHg) and 41mmHg (interquartile range, 1243mmHg), respectively.

There were no significant differences between groups in foetal blood gas values or haemodynamic parameters. Foetal arterial Po_2 decreased significantly after haemorrhage plus infusion, with similar mean±SEM decreases in control and experimental groups of 5.9±1.4mmHg and 4.5±1.5mmHg, respectively. Foetal pH also decreased significantly in both groups. After haemorrhage plus infusion there were significant increases in foetal regional cerebral and myocardial blood flows in both groups.

Adrenal blood flow increased significantly from baseline (214%, 183-294%) in the control group after haemorrhage plus infusion but not in the experimental group. No other difference in organ blood flow between control and experimental groups was observed. Significant regional variations in cerebral blood flow were not observed in either group at any time.

The authors concluded that in these initially healthy, late-gestation foetal lambs, magnesium sulfate exposure did not impair cardiac output redistribution, nor did it cause foetal death in response to maternal haemorrhage.

Other toxicity studies
No other relevant information could be found

Interaction with other compounds
No additional information could be found to indicate that magnesium sulfate would interact with any other compounds other than normally expected of the electrolyte solutions class of compounds.

Excipients used in the finished formulation
The excipients listed in the SPC are all commonly used in pharmaceutical preparations. Apart from known hypersensitivity to individual excipients, they do not pose any threat to safety or efficacy.

Drug Substance/Product Impurities
The impurity profile of magnesium sulfate complies with the ICH guidelines for impurities. There are no toxicological concerns regarding the level of these impurities.

Comment
The non-clinical discussion on toxicology is relatively detailed, discussion is made concerning the studies presented for general toxicity, genotoxicity, carcinogenicity and reproductive toxicity

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The pharmacological, pharmacokinetic and toxicological properties of magnesium sulfate heptahydrate are well known. As this active substance is well known, no further studies are required, and the applicant has provided none. An overview based on a literature review is, thus, appropriate.

The impurities and excipients in the formulation are discussed and raise no toxicological concerns.

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical data have been submitted and none are required for applications of this type. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of magnesium sulfate heptahydrate. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

It is reported in the literature that magnesium is a co-factor in many biochemical reactions. Magnesium has a direct effect on various other electrolytes, including sodium, calcium, and potassium. Magnesium homeostasis involves the kidney (primarily through the proximal tubule, the thick ascending loop of Henle, and the distal tubule), small bowel (primarily through the jejunum and ileum), and bone.

The pharmacokinetic profile of magnesium sulfate in terms of absorption, distribution, metabolism and elimination is well characterised and documented in the published scientific literature. Therefore, as a parenteral administered product where on administration there is 100% bioavailability there is no requirement for further bridging to confirm bioequivalence to products utilised in clinical studies.

IV. 2 Pharmacokinetics

The pharmacokinetics of magnesium sulfate are well-established. Studies have shown good control of convulsion for variation in route of administration, and total dose of magnesium sulfate as both prophylaxis and treatment. The two most internationally, widely used standard regimens of magnesium sulfate administration are the intramuscular (IM) regimen routinely used by Pritchard and the continuous IV regimen recommended by Zuspan on the basis of their proven clinical efficacy in the two largest magnesium sulfate trials, the Zuspan regimen includes a loading dose of 4 g IV and maintenance dose of 1 g/hr IV, while the Pritchard regimen consists of a loading dose of 4 g IV and 10 g IM, followed by a maintenance dose of 5 g IM per 4 hrs. The Zuspan regimen was later modified, to 6 g load followed by 2 g/hr continuous infusion.

The literature reports on a pharmacokinetic study performed as part of a randomised comparing intramuscular and intravenous maintenance regimens of magnesium dosing in 258 women at risk for eclampsia. The intramuscular regimen produced higher initial serum concentrations, consistent with a substantially larger loading dose. Magnesium clearance was found to be 48.1 dL/hr, (80.1 ml/minute), comparable to the glomerular filtration rate that might be expected from a cohort of women with pre-eclampsia and similar to the 42.8 dL/hr reported in another paper. The volume of distribution was 156 dL, 30–50% lower than previously reported. At steady state, magnesium concentrations in the intramuscular and intravenous groups were comparable. In conclusion the 4 g loading dose routinely used in intravenous regimens provides lower initial concentration than achieved with the intramuscular regimen which suggests that an increased intravenous loading dose (6 g) would produce initial concentrations similar to that observed with the intramuscular regimen.

To evaluate the clinical pharmacokinetic properties of magnesium sulfate when used for the treatment of pre-eclampsia and eclampsia, a study review of the available data summarised 23 studies that examined IV regimens and 9 studies that examined IM regimens. The review showed that the bioavailability for all IV regimens is complete and rapid as expected and suggests a substantial bioavailability for the IM regimens. Across all the studies the baseline serum magnesium concentrations were consistently <1 mmol/L prior to treatment.

An IV loading dose of 4–6 g was associated with a rapid doubling of this baseline concentration within half an hr of starting the injection. A maintenance infusion of 1 g/hr following a 4 g loading dose (Zuspan regimen) consistently produced mean serum concentrations between 1 and 2 mmol/L throughout the period of administration. Maintenance infusion of 2 g/hr following either a 4 or a 6 g loading dose had a higher likelihood of producing mean concentrations between 2 and 3 mmol/L with fewer fluctuations during the period of administration. Intermittent bolus injections of 2 g produced a spike in serum concentrations that fell very rapidly to almost basal levels within 2 hrs of injection. The Pritchard regimen (IM infusion) inconsistently produced serum concentrations between 2 and 3 mmol/L but the repeated IM injections resulted in more fluctuations compared with continuous IV maintenance regimens. Therefore, the preferred method of IV infusion for the product is considered appropriate for administration to adopt the Zuspan regimen.

Many studies have shown intestinal magnesium absorption is balanced against renal magnesium excretion. In times of a temporary magnesium deficit, the body depends on the availability of magnesium in bone to maintain constant serum levels. Therefore, magnesium homeostasis depends on three organs: the intestine, facilitating magnesium uptake; bone, the magnesium storage system of the body and the kidneys, which are responsible for

magnesium excretion.

The proposed route of administration of Magnesium Sulfate 20 % w/v Solution for Injection of Infusion is IV injection or infusion and therefore can be administered by the Zuspan regimen.

Absorption

IV preparations are 100% bioavailable.

The majority of magnesium is absorbed in the small intestine when taken orally by a passive paracellular mechanism, which is driven by an electrochemical gradient and solvent drag. The kidney has a vital role in magnesium homeostasis. Under normal conditions, ~30–50% of ingested magnesium is absorbed. However, the fractional absorption of magnesium rises to 80% if intake is low and falls to ~25% when magnesium intake is high.

For many years, the Zuspan regimen was used for prophylaxis and therapy of seizures. The literature remarks on failures with this magnesium sulfate regimen, and evaluated 178 random magnesium levels from 120 women, obtained 2–48 hrs following infusion of a 4 g intravenous magnesium sulfate loading dose followed by maintenance doses of 1–3 g per hr. The recommended "therapeutic" range of magnesium levels is between 4.8– 8.4 mg/dL. Only 2 of 115 women receiving maintenance infusions of 1 g/hr reached the recommended range. Only 23 (51%) of 45 women receiving maintenance infusions of 2 g/hr had serum magnesium levels in the recommended range. All women receiving a maintenance infusion of 3 g/hr had magnesium levels within the recommended range. This study evidences the benefits of changing the maintenance magnesium sulfate infusion from 1 g/hr to 2 g/hr.

A more recent pharmacokinetic analysis involving 2-compartment population pharmacokinetic (PK) model to characterize serial PK data from 92 pregnant women with pre-eclampsia who received magnesium sulfate also indicated a potential for toxicity with a maintenance infusion of 2 g/h when administered for longer duration depending on the loading dose. A total of 111 pregnant women were studied in the original publication, and a cohort of 92 pregnant women with pre-eclampsia were used in this analysis. Magnesium concentration profiles were evaluated in the context of concentrations of 1.5 to 2.5 mmol/L as the putative therapeutic range and 3.5 mmol/L as a concentration associated with toxicity. All women with pre-eclampsia received an IV infusion loading dose of 4 g magnesium sulfate over 20 minutes, followed by a continuous IV infusion maintenance dose of 2 g/h of magnesium sulfate. The IV regimens that used loading doses of 4 or 6 g, but increased maintenance doses to 2 g/h reached potentially toxic magnesium concentrations during the latter half of a 24-hr dosing interval for patients with low and median body weight and high creatinine values. However, regimens with loading doses of 8 g over 60 minutes followed by maintenance doses of 2 g/h for 10 hrs and 12 g over 120 minutes followed by 2 g/h for 8 hrs rapidly achieved potentially therapeutic magnesium concentrations without approaching the toxic range. The intravenous regimens with loading doses of 8 g over 60 minutes followed by 2 g/hr for 10 hrs and 12 g over 120 minutes, with maintenance doses of followed by 2 g/hr for 8 hrs rapidly achieved potentially therapeutic magnesium concentrations without exceeding the toxic range.

In renal failure, the IV dosages should be halved and the plasma magnesium levels closely monitored. Magnesium administration should cease if the plasma level is > 1.5 mmol/L.

Following a single intravenous loading dose of 4 g to 6 g there is an immediate but transient increase in plasma levels to 2.1-3.8 mmol/L which will fall to 1.3-1.7 mmol/L within 60 minutes.

At a constant rate, serum levels of magnesium sulfate plateau after 24 hrs at a level of 1.7 mmol/L; with an infusion rate of 2 g/h; this will occur at six to eight hrs at a level of 2.2 mmol/L. The rapid distribution of magnesium in a large pool is a buffering action that prevents accumulation and attainment of toxic concentrations in plasma.

Distribution

In healthy individuals, magnesium serum concentration is closely maintained within the physiological range of 0.65–1.05 mmol/L for total magnesium concentrations in adult blood serum and 0.55–0.75 mmol/L for ionized magnesium. Blood plasma concentration in healthy individuals is similar to serum, ranging from 0.7 to 1.0 mmol/L. Distribution of plasma magnesium levels includes 33% protein bound (25% to albumin, 8% to globulin), 60% ionized (0.4 - 0.6 mmol/L), and 6% complexed with citrate and phosphate. The total intracellular magnesium concentration is 15 mmol/L, whereas the ionized intracellular magnesium concentration ranges between 0.5 - 1.0 mmol/L (i.e. the ionic concentrations of magnesium are approximately the same outside and inside the cell).

The distribution of magnesium within the body is shown in Figure 2. About 99% of total body magnesium is located in bone, muscles and non-muscular soft tissue. About 60% of the magnesium is present in bone, of which 30% is exchangeable and functions as a reservoir to stabilize the serum concentration. About 20% is found in skeletal muscle, 19% in other soft tissues and less than 1% in the extracellular fluid. Intracellular magnesium is maintained within narrow concentration limits except in extreme situations such as hypoxia or prolonged magnesium depletion. Intracellular magnesium concentrations range from 5 to 20 mmol/L; 1–5% is ionized, the remainder is bound to proteins, negatively charged molecules and adenosine triphosphate (ATP). Extracellular magnesium accounts for ~1% of total body magnesium which is primarily found in serum and red blood cells.

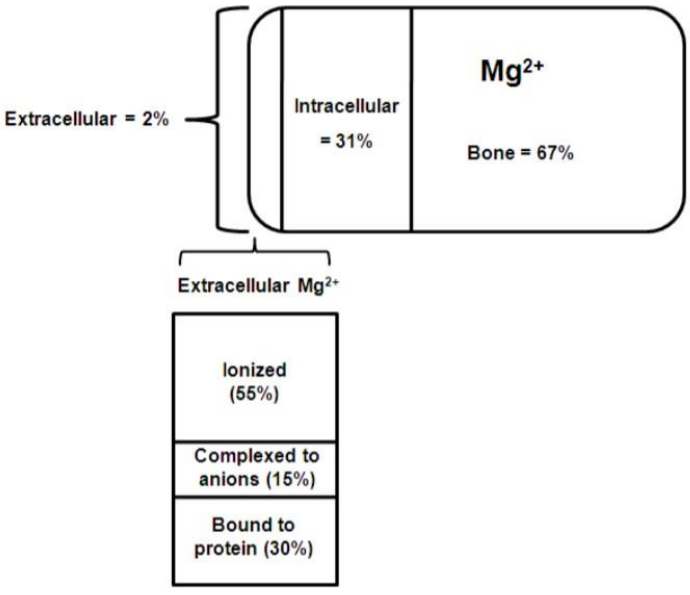


Figure 2 Distribution of chemical forms of magnesium in serum.

Similar to calcium, serum magnesium can be categorised into free/ionized, bound to protein or complexed with anions such as phosphate, bicarbonate and citrate or sulfate. Of the three fractions in plasma, however, ionized magnesium has the greatest biological activity.

Magnesium is primarily found within the cell where it acts as a counter ion for the energy rich Adenosine triphosphate (ATP) and nuclear acids. Magnesium critically stabilizes enzymes, including many ATP-generating reactions. ATP metabolism, muscle contraction and relaxation, normal neurological function and release of neurotransmitters are all magnesium dependent.

Infused magnesium is distributed rapidly throughout the entire extracellular fluid space and some is taken up by bone, but none by absorbed by red blood cells. The rapid distribution of magnesium in a large pool accounts for a buffering action that prevents accumulation and attainment of toxic concentrations in plasma. Within 90 minutes, about 50% of the infused magnesium moves into bone and other cells.

Magnesium readily crosses the placenta and foetal blood magnesium levels correlate well with maternal levels. It is believed that equilibration between mother and foetus usually occurs within two – three hrs.

A study of non-pregnant and pregnant patients reviewed the volume of distribution (Vd) of magnesium sulfate. In pregnancy the magnesium crosses the placenta and there is increase in extracellular space with the foetal absorption and the amniotic fluid space. Therefore, there is more variability in the Vd in pregnancy. When parenteral magnesium is administered it can take 2-3 hrs for the magnesium to reach equilibrium. The study reported the lowest level of magnesium in extracellular space in the pre-eclamptic patient compared to normal pregnancy (30% vs 58%). However, this analysis was performed on a pre-eclamptic patient who had also been administered diuretics and with only two normal pregnant patients. A larger study is needed to establish the intrasubject variability.

A report detailed an investigation into the short-term effects of maternal IV magnesium sulfate administration on foetal serum and amniotic fluid concentrations of magnesium and confirmed the original findings from another study. Thirty-six patients were split into 3 groups, 21 untreated controls, 10 women who received treatment for 1 hr, and 5 who received treatment for 3 hrs before foetal blood sampling. Foetal serum magnesium concentrations were significantly higher in the 1 and 3-hr groups (2.48 ± 0.1 and 4.44 ± 0.2 mg/dL, respectively) than in controls (1.67 ± 0.2 mg/dL) ($P < .0001$). The amniotic fluid magnesium concentration was significantly increased only after 3 hrs of elevated maternal magnesium levels (1.45 ± 0.2 and 2.84 ± 0.2 mg/dL in controls and 3-hr group, respectively; $P < .0001$). Magnesium levels increased in foetal serum within one hr and in amniotic fluid within three hrs after maternal IV administration. Researchers hypothesised that this is consistent with foetal urinary excretion of magnesium sulfate, which is the primary source of magnesium in the amniotic fluid. Prolonged maternal magnesium sulfate administration leads to hypermagnesemia in the newborn, with cord serum levels ranging from 70-100% of maternal concentrations.

Magnesium is able to cross the blood brain barrier and is transported via the barrier with a net flux from the blood into the parenchyma. Active magnesium transport from blood to the extracellular fluid of the brain is evidenced by its higher concentration in the cortical extracellular fluid than its concentration in the plasma- dialysate or cisternal Cerebrospinal Fluid (CSF). Magnesium administration attenuates cell death due to cytoskeletal alteration and reduces apoptosis and the expression of p53 following traumatic brain injury. Therefore, the administration of magnesium rectifies the decline in intracellular ionic magnesium levels and therefore, cellular functions.

Metabolism

Magnesium is a naturally occurring mineral, is not metabolised and is eliminated unchanged via renal metabolism.

Metabolic processes such as glycolysis, Krebs cycle, β-oxidation, active transport of ions or electrochemical coupling are regulated by magnesium dependent enzymes. The main domain of magnesium action is the activation of enzymes responsible for formation, storing and using of high-energy compounds. All reactions involving ATP require the presence of magnesium ions.

Magnesium metabolism is closely related to that of calcium and potassium, since it is required for the active transport of their ions through cell membranes. The normal adult human body contains approximately 1,000 mmols of magnesium (22-26 g).

Elimination
In individuals with normal renal function, ~74–100 mmol (1800–2400 mg) of magnesium are filtered every day. About 70–80% of plasma magnesium is ultrafilterable, and ~95% of the filtered magnesium load is subject to tubular reabsorption with 5% excreted in urine. The renal metabolism of magnesium depends to a great extent on the plasma magnesium concentration: in hypermagnesaemia, the fractional excretion of magnesium is high, while during hypomagnesaemia, it is low.

Magnesium is almost exclusively excreted in urine, with 50% of the dose excreted in the urine after 4 hrs and 90% of the dose excreted during the first 24 hrs after IV infusion (with normal renal function).

Rapid urinary excretion of magnesium has been reported by various authors. One group investigated urinary magnesium excretion during magnesium sulfate infusion in 20 women at term with mild to moderate pre-eclampsia were treated with magnesium sulfate given by IV infusion. A loading dose of 4 g magnesium sulfate was administered over 15 to 30 minutes, followed by a maintenance dose of 1 to 2 g per hr. This study demonstrated that urinary magnesium excretion increased twentyfold during magnesium sulfate, infusion; 75% of the infused dose was excreted during the infusion; by 24 hrs after the infusion, 90% had been eliminated. This is validated by the study by Pritchard that demonstrated that 99% of the magnesium in an IV bolus of 4 g of magnesium sulfate, was excreted within 24 hrs.

Researchers noted excretion of 44% of a 10 g IM dose within four hrs. This means that over 50% of magnesium remains in the body and therefore repeated dosing would expect to be cumulative and magnesium levels increase to toxic levels. However, this is not the case and with repeated dosing the level of excretion increases to compensate. Therefore, if renal function is impaired there could be reduced clearance and risk of the body magnesium reaching toxic levels. The half-life in patients with normal renal function is 4 hrs.

Small and clinically irrelevant amounts of magnesium are excreted in milk. Experiments demonstrated that intrapartum magnesium sulfate, treatment increases breast milk-colostrum magnesium levels significantly for only 24 hrs after discontinuation of the infusion. The mean maternal serum magnesium level in treated subjects was significantly higher on day 1 than controls ($p < 0.001$). On days 2 and 3, serum magnesium levels were essentially the same in treated and controls. The data on colostrum magnesium levels indicate that the breast-fed infant of a magnesium sulfate treated mother will receive more magnesium than the infant of a control mother only during the first 24 hrs after discontinuation of the magnesium sulfate infusion (At the end of infusion, maternal serum magnesium concentrations were significantly elevated, but all levels returned to control values 24 hours

after discontinuation of the infusion. The data showed serum magnesium levels of bottle-fed offspring of magnesium sulfate-treated women return to control values 48 hours after birth.

In comparison neonates, who were bottle-fed following maternal treatment peripartum, reported that the serum magnesium levels returned to control values by 48 hrs after birth.

Pharmacokinetics in target populations

Pregnancy
Magnesium sulfate was first used in the treatment of eclampsia in Germany 1906. It has since been used during the 20th century for the prevention of eclamptic seizures and continues to be used widely. During pre-eclampsia, both cardiac output and plasma volume are reduced whereas systemic vascular resistance is increased. These changes result in reduced perfusion of the placenta, kidney, liver and brain, leading to maternal and foetal morbidity and mortality.

A group of researchers investigated the changes in calcium and magnesium metabolism in normal pregnancy and pre-eclampsia, plasma, intracellular, and membrane calcium and magnesium concentrations were determined in a clinical study involving 25 control, 18 untreated healthy pregnant, and 16 pre-eclamptic women. Calcium and magnesium concentration in plasma, erythrocytes, and plasmalemmal membranes were measured with an atomic absorption spectroscope. Results showed that plasma magnesium concentration was lowered in the healthy pregnant women (0.61 ± 0.10 mmol/L; mean ± SD) as compared to female controls (0.93 ± 0.06 mmol/L, $P < 0.01$). In women with pre-eclampsia the plasma magnesium concentration was 0.63 ± 0.14 mmol/L, which was significantly lower as compared to the control subjects ($P < 0.01$). Intracellular erythrocytic magnesium concentrations were significantly decreased in normal pregnancy (1.38 ± 0.22 mmol/L) and pre-eclampsia (1.05 ± 0.18 mmol/L) versus controls (1.79 ± 0.21 mmol/L) ($P < 0.01$). The data presented in this study suggest a disturbance in the transmembrane magnesium distribution in pre-eclampsia. The demonstration of a membrane magnesium deficiency in the present study explains the successful use of magnesium in the treatment of pre-eclampsia.

Based on the reviewed evidence found in literature, adequate serum levels, without risking magnesium toxicity, can be achieved in most cases with an initial loading dose of 4 g which will increase the magnesium serum levels. Data suggests that a maintenance dose demonstrates that there is some variability depending on the extracellular space which can be altered due to weight. A maintenance dose of 1 g per hr, commonly seen in studies, has not shown any toxicity although the target magnesium level has not always been reached and further dosing and increasing to 2 g per hour proves to be effective.

Hypomagnesaemia
Given the importance of the role of magnesium in major cellular processes, the tight regulation of plasma magnesium levels is of vital importance. Hypomagnesaemia occurs because of decreased gastrointestinal absorption or increased renal magnesium excretion and is associated with a wide spectrum of diseases, including Type 2 diabetes, hypertension, osteoporosis, tetany, seizures and depression. Certain drug therapies (e.g. diuretics, aminoglycosides, cetuximab therapy and immunosuppressive agents) can result in acquired renal magnesium wasting and associated low serum magnesium levels. In severely hypomagnesaemic patients, IV supplementation can be essential to restore the patient's magnesium levels without discomforting the patient as the oral absorption is reduced.

Therefore, IV administration of magnesium sulfate allows for the direct replenishment immediate correction is mandatory as in patients with severe hypomagnesaemia. In literature, patients with serum magnesium concentrations ≤0.61 mmol/L (1.5 mg/dL) and ≤0.75 mmol/L, respectively, were considered hypomagnesaemic. Hypomagnesaemia is common in hospitalized patients, with a prevalence ranging from 9 to 65%. A particularly high incidence of hypomagnesaemia is observed in intensive care units. Furthermore, a significant association has been reported between hypomagnesaemia and oesophageal surgery. In these severely ill patients, nutritional magnesium intake was insufficient. Certain drugs have also been associated with magnesium wasting, putting the afflicted patients at an increased risk for acute hypomagnesaemia due to inadequate absorption. Such medications include aminoglycosides, cisplatin, digoxin, furosemide, amphotericin B and cyclosporine A.

A review on the function and use of IV magnesium in magnesium depleted and non-magnesium depleted patients was provided. The cardiovascular, neurological and metabolic disorders caused by magnesium deficiency are associated with an increase in morbidity and mortality and can be rapidly corrected by magnesium therapy. There is also evidence that IV magnesium alters ion channels, NMDA receptors, and calcium metabolism, causing effects that are beneficial in a range of cardiovascular, respiratory and metabolic disorders, in the absence of magnesium deficiency. In these disorders' IV magnesium sulfate is usually administered as an initial bolus varying between 8 - 16 mmol over 5 min, followed by an infusion of 2 – 4 mmol/h, to keep the plasma magnesium between 1.5 - 3 mmol/L. Magnesium is required in patients who are magnesium depleted and is also of benefit in nonmagnesium depleted patients with pre-eclampsia.

Special populations

Impaired renal function

Magnesium is renally excreted and should be used with caution in patients with renal impairment as they are at a higher risk of hypermagnesemia. With normal renal function 74100 mmol magnesium is filtered daily. The renal handling of magnesium is dependent on the plasma concentration. With the renal extraction of magnesium adapting the plasma concentration so that during hypermagnesemia there is higher fractional excretion of magnesium compared with normal. This may explain why in moderate renal impairment there is increase in the fractional excretion to compensate for the loss in renal function and magnesium serum levels are maintained.

In a cross-sectional study of 55 non-diabetic patients and 73 diabetic patients, with moderate renal impairment, serum ionised magnesium and total magnesium was investigated by measuring creatinine clearance (creatinine clearance decreasing from115 to >30 ml/min) when not treated with diuretics. Results showed significantly lower serum total magnesium and ionised magnesium values in diabetic patients with chronic renal failure than in the nondiabetic patients with chronic renal failure. Thus, in patients with diabetes, the combination of initial significantly lower magnesium values, without consequential increase of the magnesium levels during the progression of renal failure, exacerbates the risk of worsening hypomagnesaemia in comparison with the nondiabetic patients. In light of this finding, together with the knowledge of the role of magnesium (especially in hypomagnesaemia) in the pathogenesis of cardiovascular diseases, a strict follow-up of magnesium levels is recommended in diabetic patients under treatment with Magnesium sulfate.

As renal function deteriorates the quantitative magnesium excretion decreases and eventually it can no longer be compensated by the fractional excretion. This becomes apparent if the

creatinine clearance rate falls below ~20–30 mL/min. Once the creatinine clearance is below 10 ml/min there is evidence that the compensatory mechanisms are failure and it is likely that hypermagnesemia. Based on the evidence that compensation by fractional excretion is no longer possible in severe renal impairment it is proposed that that magnesium sulfate is contraindicated in renal failure (Stage 5 Renal Disease).
Studies of the serum magnesium in patient on dialysis in comparison to healthy controls indicate that dialysis patients have magnesium overload. Reported total and ionised magnesium levels of normal range of 0.65–1.05 and dialysis patients of 0.45–0.74 mmol/L.

There is evidence that patients with renal failure are at risk of developing hypermagnesemia. hence magnesium treatment is contraindicated for these patients and magnesium therapy could be considered in patients with moderately reduced glomerular filtration rate and severe magnesium deficiency. High levels of magnesium (> 4–5 mmol/L) may cause muscle weakness, reduced respiration, and in worst case cardiac arrest. Therefore, the posology in renal impairment would need to be adjusted depending on the level of glomerular filtration rate in order to reduce the risk of magnesium overload. Caution is advised in the repletion of magnesium in patients with abnormal kidney function (defined as creatinine clearance less than 30 mL/min). These patients are at risk of hypermagnesemia. Studies recommend reducing the magnesium dose by 50% and closely monitoring magnesium levels in these patients.

Considering that administration of magnesium over a longer duration leads to increased risks that the compensatory mechanisms of fractional excretion cannot be maintained and this would lead to accumulation of magnesium the dosage should be limited within the 48 hours to compensate for the slower elimination in renal impairment.

Diabetes
Type 2 diabetes mellitus is often associated with hypomagnesaemia and incidence rates of 13.5–47.7% have been reported. Magnesium deficiency has also been linked to the development of the disease as well as its severity: the lower the magnesium level the faster the deterioration of renal function in Type 2 diabetics. The mechanisms whereby hypomagnesaemia may induce or worsen existing diabetes are not well understood. It has been suggested that magnesium regulates cellular glucose metabolism directly because it serves as an important cofactor for various enzymes and acts as a second messenger for insulin. It was also observed that insulin enhances intracellular magnesium uptake and this in turn mediates diverse effects ascribed to insulin. Furthermore, hypomagnesaemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective post-receptor insulin signalling and/or altered insulin–insulin receptor interactions and thus aggravate insulin resistance.

Impaired hepatic function
Severe hypermagnesaemia and hypercalacaemia developed in 2 patients with hepatic encephalopathy following the administration of magnesium sulfate and both cases were fatal. In both patients, hypermagnesaemia developed as renal function deteriorated and therefore, it is presumed that hypermagnesaemia resulted from failure of renal magnesium excretion. It was recommended that patients with liver disease who might develop renal impairment, or in whom renal failure is established, should not be given magnesium sulfate as serious magnesium toxicity can occur. Magnesium sulfate solution should not be used in hepatic coma if there is a risk of renal failure.

Gender
There has been one reported prospective randomised study that analysed the potential difference in gender on the pharmacokinetics of magnesium sulfate. This study assessed the prophylactic effect of magnesium supplementation at a fixed dose of 5 g IV in adult patients, male (36) and female (23), who were receiving cisplatin-based chemotherapy. There were no statistically significant differences in the distribution of variables in the magnesium supplementation and control group, including sex (male: 51.6% vs. 71.4%, P=0.12). There are no reported differences in magnesium distribution or elimination between genders across the studies.

Race
The effect of race/ethnicity on magnesium sulfate use during pregnancy has not been widely studied. A subgroup analysis of a multicentre clinical trial analysed the effect of race/ethnicity in maternal/infant outcomes after magnesium sulfate neuroprotection. Pregnant women at risk of preterm birth and were randomized to either receive magnesium sulfate (922 women) or placebo (972 women) (45.0% African-American, 36.2% Caucasian, 17.8% Hispanics, and 1.0% Asians). The risk of side effects to magnesium sulfate administration was significantly higher in mothers of Hispanic ethnicity, with the risk of other perinatal outcomes not being significantly different among racial/ethnic groups. Furthermore, the neuroprotective effect of magnesium sulfate did not seem to be impaired by race/ethnicity. The study does not detail whether there was any standardisation of the dose or duration of use and the sample power of each population was limited. Whether specific racial/ethnic groups require closer surveillance for early signs of magnesium toxicity, or whether these patients may benefit from lower dosage of magnesium sulfate, needs to be studied.

Weight
Magnesium sulfate treatment is influenced by body mass index (BMI). In a clinical study, the patient under investigation had a BMI of 31.2 kg/m^2 before pregnancy, which is classified as obesity grade II based on the Asia Pacific criteria. It has been suggested that women with high BMI have lower circulating levels of magnesium and it remains subtherapeutic up to 18 hrs. Around 40% of circulating magnesium is protein bound and the unbound fraction diffuses into extravascular and extracellular spaces. In pregnant women, the distribution of magnesium sulfate reaches plateau (2.5–4.4 mg/dL) between the 3 and 4 hrs.

Another report concluded that weight and serum creatinine were significant covariates affecting magnesium clearance and volume distribution and that slow dose titration of the maintenance infusion across a range of body weights (65, 75, 85, 95, and 105 kg) and creatinine concentrations (0.5, 0.8, and 1.2 mg/dL) is advised.

In a case study, following C-section, the patient's blood pressure was raised to 190/120 mmHg with +2 proteinuria and underwent administration of a loading dose of 4g magnesium sulfate continued by 1g per hr as maintenance. After 24 hrs of magnesium sulfate infusion, treatment was stopped and the patient had a seizure 4 hrs later with serum magnesium levels of 4.3 mg/dL. Following a repeated dose of magnesium sulfate 40% 1g/hr for 24 hrs, the convulsions had stopped. Therefore, there is a suggestion that doses may need to be increased for women with BMI exceeding 35 kg/m^2, especially in antepartum in order for the magnesium to be distributed before reaching the equilibrium. However, as this is a single case study, the results are not statistically significant to justify any dosing adjustment for women who are overweight or obese.

A report on the study of the pharmacokinetics and placental transfer of magnesium sulfate in pregnant women to determine key covariates that impact the pharmacokinetics was provided. Women who were prescribed magnesium sulfate for pre-eclampsia, preterm labour, or extreme prematurity. Women received a 4 g loading dose and 2 g/hr maintenance dose. Pharmacokinetic profiles of 111 pregnant women were analysed. Magnesium clearance was 3.98 L/hr in pre-eclamptic women and 5.88 L/hr non-pre-eclamptic women. Steady-state concentration of magnesium was 7.2 mg/dL in pre-eclamptic women compared with 5.1 mg/dL in non-pre-eclamptic women. Maternal weight significantly impacted time to steady state. The ratio of the mean umbilical vein magnesium level to the mean maternal serum magnesium level at the time of delivery was 0.94 ± 0.15.

Elderly
Very little published data exists concerning the use of magnesium sulfate for the treatment of magnesium deficiency in hypomagnesaemia in the elderly population. There are no special recommendations for use in the elderly but caution needs to be exercised in this population due to the risk of renal impairment.

Children
Very little published data exists concerning the use of magnesium sulfate for the treatment of magnesium deficiency in hypomagnesaemia in the paediatric population. However, demographic data from the studies investigating the use of magnesium sulfate in pre-eclampsia and eclampsia have reported age of 22 yrs ±5 and one study stated ages ranging from 17-24yrs, indicated that studies in pregnancy include patients younger than 18 yrs. A large randomised trial treating women with severe pre-eclampsia with magnesium sulfate only excluded patients younger than 16 yrs due to difficulties obtaining consent, there were no specific findings reported in the younger patients. A further prospective trial reported 138 women less than 15 years treated with magnesium sulfate. In these studies, there were no specific reports on differences related to the children.
There is no contraindication to the use of the drug in children.
No further case reports in adolescents under 18 years are reported throughout literature.

Comment on paediatric information
Other currently approved Magnesium sulfate solutions for infusion do not contain specific recommendation for use in the paediatric population. Since this application was submitted under Regulation 54, the applicant was requested to provide evidence of efficacy and safety in the proposed population. The wording of the SmPC reflects the limited scientific literature on the paediatric population.

Pharmacokinetic Interactions
Magnesium also acts as a calcium channel antagonist, and therefore, can cause bradycardia, hypotension, electrocardiogram changes (i.e., P–Q interval prolongation and widened QRS complex), and at very high levels, cardiac arrest. Hypocalcaemia can also result from magnesium sulfate therapy by inhibition of parathyroid hormone. Therefore, infusion rates of magnesium sulfate should be reduced where there are signs of changes to cardiac electrical conduction.

With respect to the effect of magnesium on calcium uptake, some studies have described a decrease in calcium absorption with increased magnesium. Magnesium inhibits calcium induced myocardial muscle contraction by, inhibiting the release of calcium from the sarcoplasmic reticulum, increasing the uptake of calcium by the sarcoplasmic reticulum (by stimulating the calcium-ATPase activity) and competing with calcium at certain binding sites on troponin C and myosin. Unlike the synthetic calcium-blockers, increasing extracellular

magnesium has not been shown to block the entry of calcium into the cell through the slow channel, although increasing intracellular magnesium experimentally inhibits calcium entry through the dihydropyridine-sensitive channels. While magnesium has a calcium inhibitory effect, at plasma levels < 10 mmol/L, it appears to have no negative inotropic effect.

Intracellular magnesium augments inward rectification of potassium (i.e. allows potassium to pass into the cell more readily than out of the cell by blocking potassium channels from the inner surface of the sarcolemma). Inward rectification of potassium is inhibited when magnesium is sufficiently reduced, increasing early after depolarizations (i.e. oscillations in the transmembrane potential occurring before the cell has had a chance to repolarised fully) leading to repetitive membrane depolarisations (i.e. triggered activity) which may manifest clinically as polymorphic ventricular tachycardia (an effect which is suppressed by IV magnesium).

In addition, vitamin D may influence the intestinal absorption of magnesium. High doses of 1,25-dihydroxy vitamin D increase the absorption of magnesium, but magnesium is also absorbed independently of vitamin D and the intestinal vitamin D receptor.

IV.3 Pharmacodynamics

Pharmacodynamic effects
Magnesium is one of the body electrolytes and therefore is involved in may intracellular physiologically processes. It is a counter ion for energy rich ATP and acts as a co-factor in various enzymatic reactions. ATP is needed for glucose use, synthesis of fats proteins and nucleic acids and therefore imbalances in magnesium metabolism includes functions of muscle activity and neuromuscular transmission.

Cardiovascular effects
The cardiovascular actions of the magnesium ion at pharmacological concentrations (1.5 - 2.5 mmol/L) include peripheral, coronary and systemic vasodilatation, platelet inhibition, and antiarrhythmic effects. Many cardiovascular disorders are associated with changes in magnesium levels; in particular, those affecting the myocardium and involving blood pressure control. Both left ventricular hypertrophy and high blood pressure have been linked to hypomagnesaemia. Magnesium inhibits basal, myogenic and hormone induced smooth muscle contraction and has a direct vasodilator effect. Magnesium blocks calcium entry into vascular smooth muscle cells via voltage- and receptor operated channels and it diminishes the reactivity of these cells to a variety of pressor agents. In the same way, magnesium competes with calcium to inhibit the contractility of coronary arteries Magnesium deficiency leads to an increase in the concentration of calcium into vascular smooth muscle cells, which in turn can result in increased arteriolar tone and coronary spasm.

Hypomagnesaemia is a possible cause of arrhythmia, however, it is difficult to establish a direct link between magnesium deficiency and arrhythmia because the correlation of serum and cardiac magnesium concentration is poor. To complicate matters further, hypomagnesaemia is closely related to hypokalaemia, which itself is arrhythmogenic. In addition, magnesium deficiency exacerbates potassium mediated arrhythmia, in particular in the presence of digoxin intoxication. Nonetheless, the therapeutic role of magnesium in this indication has been thoroughly studied, and most investigations revealed a favourable effect when keeping magnesium concentrations within the physiological range, an effect which was enhanced when both magnesium and potassium concentrations were adjusted.

Pre-eclampsia is characterized by haemoconcentration, vasoconstriction with increased peripheral resistance and reductions in cardiac output, plasma volume and prostacyclin synthesis. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, and thus the shift in balance of the thromboxane/ prostacyclin ratio might end-up favouring vasoconstriction and platelet aggregation. Magnesium appears to trigger the release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, which is synthesized by the endothelium of vessels. Magnesium has been shown to improve endothelial function in pre-eclampsia. This may be due to the direct vasodilatory properties of magnesium and/or to the ability of magnesium to stimulate release of the endothelial vasodilator prostacyclin, which induces vasodilation and inhibits platelet adherence and aggregation. Therefore, an increase above normal levels of magnesium in serum has been shown to inhibit platelet aggregation.

A report on the evaluation of hemodynamic effects of magnesium sulfate in pre-eclamptic patients was provided. Fifteen pre-eclamptic patients at 32.4 ± 3.3 (mean ± SD) weeks' gestation were hemodynamically monitored in the lateral recumbent position by thoracic electrical bioimpedance before and during high-dose magnesium sulfate bolus and infusion. At baseline the systemic vascular resistance index was 2465 ± 718 F ohm/m2 and the cardiac index was 3.6 ± 1.0 L/min/m2 for the pre-eclamptic patients. Magnesium sulfate infusion of 5 g bolus over 20 minutes followed continuous infusion of 3 g/h resulted in a rapid, sustained fall in systemic vascular resistance and a rise in cardiac index in the pre-eclamptic patient. This effect was evident at least 4 hrs after initiation of the bolus and infusion. In pre-eclampsia, acute magnesium sulfate administration improved endothelial function and a rapid fall in systemic vascular resistance followed. Subsequently, blood pressure decreased transiently and cardiac index increased. The dose given was higher than standard dose regimen enhancing the cardiac effects. The study did not report the serum magnesium concentrations to determine if the patients were within normal therapeutic range, however there were no reported symptoms of hypermagnesemia.

There is evidence that magnesium serum levels above 12 mg/dl results in abnormal cardiac conduction. The effect of magnesium deficiency on cardiac rhythm is clear from symptoms of hypomagnesaemia. Studies have indicated that magnesium slows atrioventricular nodal conduction and suggested a relationship between magnesium and the prognosis of coronary artery disease. Low serum magnesium has been found to lead to proarrhythmic effects with increased risk of atrial fibrillation. As an antagonist of calcium the increased magnesium would leads to decreased calcium. Symptoms of hypocalcaemia can lead to prolonged QT interval. As a result, with an imbalance between calcium and magnesium levels, there is a potential risk of ECG changes.

A randomised, double blind, placebo-controlled trial of 2316 patients with suspected acute myocardial infarction. Patients received placebo or magnesium sulfate intravenously (8 mmol) for 5 min before initiation of thrombolytic therapy, followed by an infusion (65 mmol) for the next 24 hrs. Mortality from all causes was 7.8% in the magnesium group and 10.3% in the placebo group (2p=0.04), a relative reduction of 24% (95% confidence interval 1-43%). Within the coronary care unit, the incidence of left ventricular failure was reduced by 25% (7-39%) in the magnesium group (2p=0.009). The outcomes in this study indicate magnesium sulfate has effect on the cardiac muscle. Magnesium is known to interact with potassium and it may exacerbate potassium-mediated arrhythmias by a complex interaction which modifies the action potential at nerve endings. The mechanism by which magnesium acts is probably by slow inward calcium current block, which decreases sinus node rate, prolongs AV conduction time and increases AV node refractoriness without major changes in ventricular

physiology. There is evidence in studies that AV node conduction is slowed with administration of magnesium.

Respiratory Effects
Patients receiving magnesium sulfate medication demonstrate markedly increased sensitivities to the administration of both depolarizing and nondepolarizing muscle relaxants because of the inhibitory effect of the magnesium ion at the myoneural junction. Magnesium is thought to act centrally as a general cortical depressant and peripherally by a variety of mechanisms. At the presynaptic membrane it appears to act by decreasing the release of acetylcholine in response to motor nerve impulses, and at the postsynaptic membrane by reducing the sensitivity of the motor end-plate to acetylcholine and by decreasing the amplitude of the motor end-plate potential.

Pulmonary function was studied in ten pre-eclamptic women in labour receiving continuous IV infusions of magnesium sulfate. Results showed a significant decrease in pulmonary function tests in term pre-eclamptic patients receiving magnesium sulfate for seizure prophylaxis. There was a decrease in functional vital capacity and forced expiratory volume at 1 second. Similarly, there was no significant change in the forced expiratory volume at 1 second/functional vital capacity ratio. Furthermore, there was an observed decrease in respiratory function is due to a generalized respiratory muscle weakness. As a consequence of the peripheral actions of magnesium sulfate on nerve and muscle, smaller doses of neuromuscular blocking agents are generally required.

Renal system effects
There is no human data to evidence the renal system effects of magnesium. A discussion is provided in the nonclinical overview of the effects on the renal system seen in animals.

Drug-drug interactions
A study was provided that investigated the frequency of possible cardiopulmonary drug-drug interactions among pregnant women who received intrapartum magnesium sulfate. The frequency of cardiopulmonary drug-drug interactions was compared among women who did, and did not, receive aminoglycoside antibiotics, antacids / laxatives, calcium channel blockers, corticosteroids, diuretics, neuromuscular blocking agents, and vitamin D analogues, all of which are contraindicated for patients receiving magnesium sulfate. The majority of magnesium sulfate drug interactions occurred among women who were concomitantly prescribed calcium channel blockers (e.g., nifedipine), diuretics (e.g., furosemide), and antacids / laxatives (e.g., magnesium hydroxide). It was found that the concomitant administration of magnesium sulfate and furosemide was associated with an increased risk of cardiopulmonary adverse events, which may have occurred as a consequence of profound fluid loss and electrolyte imbalances. Antacids could increase the serum calcium and therefore lead to the antagonistic effect on magnesium.

Neuromuscular blockers
Parenteral administration of magnesium sulfate potentiates the effects of competitive and depolarising neuromuscular blockers. The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive. Similarly, parenteral magnesium sulfate and nifedipine have been reported to have additive effects. Magnesium salts have been reported to have an accelerating effect on nondepolarising neuromuscular blocking drugs, such as rocuronium or vecuronium muscle relaxants and lead to prolonged respiratory depression. Similar action is seen with aminoglycoside antibiotics.

The vasodilatory properties of magnesium sulfate could increase the risk of hypotension with anaesthesia although there no case evidence of the use.

Vasodilatory Agents
Agents used to treat peripheral vascular disease such as phentolamine blocking noradrenaline, increasing myocardial contractions and dilating blood vessels may lead to a synergistic effect with magnesium sulfate which is also thought to lead to a vasodilatory effect. Mean arterial pressure and urinary protein measurements in patients treated in combination with phentolamine vs magnesium sulfate alone was significantly lower with combined treatment, suggesting there may be benefit with the use in combination to support the reduction in blood pressure in during pregnancy.

Another recent retrospective study supported the above finding, to show that further combination treatment of magnesium sulfate with phentolamine and nifedipine may improve maternal and neonatal outcomes as the combined anti-hypertensive agents. This study had limited monitoring measurements to evaluate the true outcomes on the effect of this combination limiting the adverse reactions and the improvement in the hypertensive state in pre-eclamptic patients.

Calcium channel blockers
Occasionally, a patient is simultaneously exposed to magnesium sulfate and nifedipine and because both agents are calcium channel blockers, some interaction could be expected. A depressive effect on blood pressure (increased hypotensive effect) has been observed when these agents are combined. Case reports suggest that calcium channel blockers like nifedipine may potentiate the neuromuscular blockade effect and therefore suggesting a degree of toxicity of magnesium sulfate leading to life-threatening complications. A team of researchers, studied nifedipine in women who were receiving magnesium sulfate, and found effective blood pressure control in 96% of women without undesirable side effects and no case of hypotension in the 24 cases studied. It would therefore appear that while a theoretical risk of interaction does exist, in practice this may be relatively uncommon.

A study where nearly 1 in 10 pregnant women simultaneously received magnesium sulfate and a calcium channel blocker there were two reports of severe maternal hypotension and two cases of transient neuromuscular blockade and two (4%) experienced a cardiopulmonary drug-drug interaction.

Diuretics
In the same study, a cardiopulmonary adverse event occurred among 13 of 155 (8%) women who received one or more magnesium sulfate interacting drug. None of the 531 women who did not receive an interacting drug experienced a cardiopulmonary adverse event (Fisher's Exact test P<0.001). Twelve of the 13 (92%) cardiopulmonary adverse events were documented among pregnant women who simultaneously received a diuretic agent. The most commonly identified diuretic was furosemide, which accounted for 11 (85%) of the cardiopulmonary adverse drug-drug interactions. Three of 53 (6%) women who received furosemide with magnesium sulfate experienced a cardiac arrest as compared to 0 of 618 who did not receive furosemide (Fisher's Exact test P<0.001). Additionally, 9 (17%) furosemide treated women developed acute respiratory failure as compared to 2 of 618 (0.3%) women who did not receive furosemide (Fisher's Exact Test P<0.001).

Concomitant administration of the diuretic agent furosemide was associated with higher rates of cardiac arrest and acute respiratory failure.

Diuretics are likely to lead to electrolyte imbalance and have an impact on the magnesium elimination rate. Similar interaction could be present with laxative use.

Comment
A discussion on drug-drug interactions has been provided and drug-drug interaction statements in the product information are appropriately supported by refence to acceptable published literature.

IV.4 Clinical efficacy

Magnesium deficiency in hypomagnesaemia
The reported normal serum concentration of magnesium is 1.5 to 1.9 mEq/L. Total magnesium in average 70 kg adult is approximately 1000 – 1120 mmol (24 g). Serum magnesium and the magnesium tolerance test are most widely used to assess the magnesium status of a patient. The serum magnesium is easily available but may not adequately reflect the body magnesium stores because of the physiological distribution of magnesium. Therefore, the magnesium tolerance test is a more accurate way to assess magnesium status. The test is performed by measuring the magnesium in a 24 hrs urine collection, then administer parenteral magnesium (often 2.4 mg/kg of lean body weight given over the initial 4 h of the second urine collection), and then repeat the 2 hrs urine collection. Patients with a normal magnesium status will excrete the magnesium load during the second urine collection. Retention of more than 20% of the administered magnesium is suggestive of deficiency. Symptomatic hypomagnesaemia is associated with a deficit of 0.5– 1 mmol/kg. Clinical signs of hypomagnesaemia include tremor, agitation, depression, cardia arrhythmia and electrolyte changes including hypokalaemia and hypercalcaemia. Early symptoms include nausea and vomiting, fatigue and muscle weakness and this progresses into numbness, tingling, muscle cramps and seizures due to changes in brain electrical activity and changes in heartbeats.

The magnitude of magnesium deficiency is said to be 1–2 mEq/kg of body weight. In general, mild hypomagnesaemia with no or only mild symptoms can be treated with oral supplements, whereas parenteral magnesium supplementation is indicated if magnesium concentration is < 0.5 mmol/L or if the patient presents with significant symptoms. Magnesium depletion is characteristic of critically ill patients and can be associated within increased mortality control of the serum magnesium concentrations to within normal range. From review of the studies in the treatment of symptomatic hypomagnesaemia a dose of 1-2 g initial bolus followed by an infusion of 4-8 g over 12-24 hours proved effective. For critically ill patients with mild to moderate hypomagnesaemia the administration of 1 g (8 mEq) of IV magnesium per hr will increase the serum magnesium concentration by 0.15 mEq/L within 18 to 30 h. In cases of severe hypomagnesaemia where serum concentrations are less than 1 mg/dl. IV doses may be as much as 4-8 g per hours to achieve the necessary return to normal serum range.

The results of several controlled trials indicate that magnesium supplementation can reduce the incidence of hypomagnesaemia.

A review of the medical records over a 23-month period of patients treated for mild to moderate hypomagnesaemia showed an increase in the average serum magnesium concentration from 1.62 mEq/L (SD: 0.18 mEq/L) to 1.98 mEq/L (SD: 0.28 mEq/L). The

study defined the primary effectiveness outcome as a target serum magnesium concentration (>2 mEq/L) which was reached by 51 (59.8%) of patients treated compared to an expected 89 (P < .0001). When the length of the infusion time was evaluated, there was no significant difference between shorter target infusion time (<1 g per hr) or longer than target infusion time. Therefore, the length of the infusion time did not predict the outcome in achieving the required serum concentrations. Less than two-thirds of patients analysed achieved the target serum concentration within the 24 our period. However, the infusion rate was not consistent and 58.4% of patients received more than 1 g per hr which would reduce the uptake of magnesium into cells, although longer infusion times of less than 1 g per hr did not show a significant difference in the overall target serum concentration. Patient specific morbidities can alter magnesium concentrations which in this study was not accounted for. Furthermore, the measurements were taken after 24 hrs and there were no interim measurements at 4-6 hrs to determine the true percentage increase in the concentration of serum magnesium.

A prospective randomised study assessed the incidence of hypomagnesaemia and the prophylactic effect of IV magnesium supplementation at a fixed dose of 5 g in adult patients who received cisplatin-based chemotherapy. Cisplatin, a widely used antineoplastic agent, can cause hypomagnesaemia because of renal tubular damage and urinary magnesium wasting. Serum magnesium levels <1.8 mg/dL were considered to indicate hypomagnesaemia. There were no observed cases of magnesium intoxication in the supplementation group. Magnesium supplementation at a dose of 5 g per cycle only partially compensated for cisplatin-induced magnesium loss. This finding may suggest the need for an even higher dose of magnesium supplementation for complete compensation in cisplatin induced hypomagnaesaemia.

Beneficial effects of magnesium supplementation in patients with hypomagnesaemia due to heart failure. Hypomagnesaemia leads to change in cardia electrical activity and hypokalemia. The study investigated the number of ventricular arrhythmias decreased significantly in the magnesium-treated subgroup, but not in the placebo group. Serum magnesium increased from 0.71 6 0.13 to 0.84 6 0.14 mmol L21(P = 0.01).

A double blinded randomised trial treated AIDS patient with CMV disease with magnesium sulfate who were also treated with foscarnet which is known to induce hypomagnesaemia. The treated patient reported lower incidence of hypomagnesaemia symptoms such as nausea, numbness of fingers or lips, twitching or spasms, anxiety or nervousness, headaches, flushing or fatigue. The magnesium sulfate treated group exhibited less foscarnet induced hypomagnesaemia but not the foscarnet induced hypocalcaemia although there was an increase in the PTH levels. This study was a short study of 4 days and therefore it is difficult to infer and specific results of the long-lasting effects on the magnesium and calcium imbalance induced by foscarnet is required.

Similarly, cisplatin induced hypomagnesaemia was investigated with the treatment of magnesium sulfate. There was a gradual decline in serum magnesium in both treated and untreated groups, however the gradient in the magnesium sulfate treated group was lower and there was an overall lower loss of magnesium. Furthermore, after the 5^{th} course of cisplatin therapy there was still no significant difference from baseline and the mean magnesium level. Although there was some hypomagnesaemia still evident in the treated group, there is evidence of some compensation of cisplatin related magnesium loss and therefore supplementation could be beneficial.

Prevention and control of seizures in severe pre-eclampsia
For eclamptic seizure prophylaxis in pre-eclamptic women, magnesium sulfate has been shown to be superior to phenytoin, lytic cocktail (usually chlorpromazine, promethazine and pethidine) and diazepam, as well as causing fewer adverse effects. The Collaborative Eclampsia Trial provides evidence of the superiority of magnesium sulfate therapy for treatment of recurrent seizures in eclampsia. . In addition, magnesium sulfate reduced the risk of maternal death by a quarter compared with those treated with diazepam, RR 0.7 (95% CI 0.4, 1.4) and reduced the risk of maternal death by half compared with those treated with phenytoin, RR 0.5 (95% CI 0.2, 2.0).

To determine the effect of pre-eclampsia, magnesium sulfate prophylaxis, and maternal weight on labour induction in women with pre-eclampsia, a retrospective study of 55 pre-eclamptic women and 176 non-pre-eclamptic women requiring labour induction over an 18 month period was conducted retrospectively. All patients with severe pre-eclampsia received IV magnesium sulfate to prevent convulsions. Women with pre-eclampsia had a significantly higher rate of failed induction than did those without pre-eclampsia ($p = 0.01$). However, the women with pre-eclampsia had a higher mean maternal weight and an increased use of magnesium sulfate, and labour was induced at earlier gestational age than in those without pre-eclampsia ($p < 0.05$). Observations seem to support delaying the initiation of magnesium sulfate therapy for seizure prophylaxis in order to help accelerate labour induction in women with pre-eclampsia.

Prevention and control of recurrent seizures in eclampsia
Several randomized trials were reported comparing the efficacy of magnesium sulfate with other anticonvulsants in eclamptic women. In these trials, magnesium sulfate was compared with diazepam, phenytoin, or a lytic cocktail. Only one of these trials was multicentre and had an adequate sample size. The results of these trials have been summarised in the literature. Nineteen randomized controlled trials, five retrospective studies, and eight observational reports were reviewed. The overall results of these studies demonstrate that magnesium sulfate is associated with a significantly lower rate of recurrent seizures (RR 0.41; 95% CI, 0.32-0.51), and lower rate of maternal death (RR 0.62; 95% CI, 0.39-0.99) than that observed with other anticonvulsants. Therefore, there is evidence indicating that magnesium sulfate is the best available anticonvulsant for patients with eclampsia.

A comparator international multi-centre, randomised trial of 1680 women with eclampsia was analysed comparing standard anticonvulsant regimens. Primary measures of outcome were recurrence of convulsions and maternal death.

Magnesium sulfate reduced the risk of recurrent seizures in eclamptic women by 52% when compared to diazepam and a lower relative risk of developing recurrent convulsions (5.7% vs 17.1%). However, there was no significant difference in maternal mortality between the treatment groups. Women given magnesium sulfate had a 67% lower relative risk of developing recurrent seizures when compared to phenytoin. Maternal mortality was non-significantly lower among women allocated magnesium sulfate. Women allocated magnesium sulfate were also less likely to be ventilated, to develop pneumonia and to be admitted to intensive care facilities than those allocated to phenytoin. The babies of women who had been allocated magnesium sulfate before delivery were significantly less likely to be intubated at the place of delivery, and to be admitted to a special care nursery, than the babies of mothers who had been allocated phenytoin. The publication of this clinical trial significantly increased the use of magnesium sulfate versus other anticonvulsants in the United Kingdom and Ireland where the reported use increased from 2% to 40%.

Through a summary of published evidence, six randomised trials were reviewed, involving 972 women, to assess the effects of magnesium sulfate (IV or IM administration) compared with phenytoin when used for the care of women with eclampsia. Most of the women in the studies received a 4 g loading dose followed by maintenance therapy of 1 g per hr for a duration of 24 hrs. The comparison was in terms of maternal mortality, recurrence of convulsions and other serious morbidity that could lead to death.

The reported risk ratio score for the use of magnesium sulfate rather than phenytoin for the recurrent of seizures with phenytoin treatment was 66%. Although there was no significant difference in maternal mortality with a risk ratio score of 50% between the two treatments there was trend for reduced maternal mortality. Overall, the studies provided supportive evidence that magnesium sulfate could reduce the occurrence of seizures in eclampsia, and there is evidence of reduction in maternal mortality although this was not superior to phenytoin.

Review of several randomized trials have compared the efficacy of magnesium sulfate with other anticonvulsants in women with eclampsia, and the rates of recurrent seizures and maternal death were significantly reduced with magnesium sulfate as compared with other anticonvulsants.

In a prospective randomized study, women with eclampsia were assessed for the effectiveness of a reduced duration (12 hrs) of magnesium sulfate administration for eclampsia. All patients received a magnesium sulfate loading dose (4 g, IV), followed by maintenance doses (1 g/hr) for 12 hrs (study group) and 24 hrs (control group). The primary outcome was recurrent convulsions after completion of magnesium sulfate therapy. No convulsions recurred in either group after the completion of treatment. For women with eclampsia, 12 hrs of magnesium sulfate could effectively prevent recurrent convulsions.

There is evidence that administration of magnesium sulfate can prevent the recurrence of seizures in eclampsia and therefore there is subsequent beneficial effects for the neonatal outcomes. There is some variation in the evidence for a reduction of maternal mortality between trials with some reports suggesting there is no significant difference compared to alternative anticonvulsants. However, the impact of the neonatal outcomes needs to be considered together with the overall outcomes, however, there is evidence that magnesium sulfate can improve the APGAR scores after 5 minutes and reduce the need for intubation and neonatal critical care. A randomized, triple-blind clinical trial was conducted to compare serum magnesium levels during intravenous infusion of magnesium sulfate at 1gram/hour versus 2grams/hour as a maintenance dose to prevent eclampsia in 62 pregnant and postpartum women with severe pre-eclampsia. An IV loading dose of 6 g of magnesium sulfate was administered over 30 minutes in both groups. The patients were then randomized to receive a maintenance dose of either 1 or 2g/hr for 24hrs. Serum magnesium levels were higher in the 2 g/hr group, with a statistically significant difference from 2 hrs after the beginning of the magnesium sulfate infusion ($P < 0.05$). No cases of eclampsia occurred and side effects were more common in the 2-gram/hour group however, all were mild. This study showed clear evidence that magnesium sulfate therapy at the maintenance dose of 1g/hr was just as effective as the 2 g maintenance dose reduced the incidence of seizures, with fewer side effects. However, as there were no seizures reported in either group, without a vehicle control group it is difficult to determine if there is an absolute prevention of seizures from magnesium treatment.
Considering the drawbacks in the above trial, a randomised controlled trial, investigated whether magnesium sulfate reduces the occurrence of eclampsia in women with severe pre-

eclampsia. Six hundred and eighty-five women with severe pre-eclampsia were randomised to receive either placebo (saline) or magnesium sulphate intravenously (4 g followed by 1 g/h maintenance dose). Of 345 women who received magnesium sulfate, 0.3% developed eclampsia and in the placebo group, 3.2% developed eclampsia (RR 0.09; 95% CI 0.01-069; P = 0.003). In this study, the use of IV magnesium sulphate in the management of women with severe pre-eclampsia significantly reduced the development of eclampsia.

One of the largest placebo-controlled trial considered the primary outcome of eclampsia before delivery and in still births. Secondary outcomes included maternal morbidity, labour complications and neonatal morbidity and adverse effects. There were significantly fewer eclamptic convulsions amongst the women treated with magnesium sulfate than placebo control group (40, 0·8%, vs 96, 1·9%; i.e., fewer women with eclampsia per 1000 women, 95% CI 7–16 women; p<0·0001). This represents a lower relative risk for convulsions and the calculated to NNT for women with severe pre-eclampsia as 63 and for without severe pre-eclampsia 109. The rate of maternal mortality was lower in the magnesium sulfate treated group. There were no clear differences in the maternal morbidities nor in neonatal deaths when administered before delivery. There was a clear improvement in the risk of placental abruption in the magnesium sulfate treated group with 12 fewer women per 1000 women, representing a 27% lower relative risk. The results demonstrate that magnesium sulfate is effective in reducing the risk of eclampsia with 11 per 1000 fewer women treated with magnesium sulfate have an eclamptic convulsion. There results were consistent even when considering subgroup analysis, regardless of the severity of pre-eclampsia. Respiratory depression and arrest in relation to magnesium sulfate treatment was reported but the numbers were small and this did not report to make an overall difference to the maternal morbidity scores.

IV. 5 Clinical safety

The majority of adverse effects reported are related to toxicity with important signs related to the neuromuscular blockade including loss of the deep tendon reflexes and respiratory depression. Early signs and symptoms of magnesium toxicity include flushing, nausea and vomiting, thirst, muscle weakness, somnolence, dizziness, confusion and slurred speech. The administration can cause irritation at the injection site. More serious side effects are rare but signs of toxic effects of magnesium sulfate include the loss of the patellar reflex (typically occurring at a serum concentration of 8 -10mEq/L) and respiratory depression (>13 mEq/L). With increased monitoring, the risk of serious side effects can be mitigated.

The submitted literature reviewed the well-established PD, PK, efficacy and safety effects of magnesium sulfate and presented a clinical assessment supporting the use of Magnesium Sulfate 20% w/v Solution for Injection or Infusion in the following indications:

- Treatment of magnesium deficiency in hypomagnesaemia
- Prevention and control of seizures in severe pre-eclampsia.
- Prevention and control of recurrent seizures in eclampsia

Magnesium, an essential body electrolyte, is the fourth most abundant cation in the human body. It is a cofactor in numerous enzyme systems and is involved in phosphate transfer, muscle contractility and neuronal transmission. Magnesium sulfate, an inorganic and commercial preparation used in the parenteral form and is one of the most commonly prescribed intravenous medications in obstetrics. The reported normal serum concentration of magnesium is 1.5 to 1.9 mEq/L.

The product is a sterile IV solution to be administered intravenously for 100% bioavailability. One of the most internationally and widely used standard regimen of magnesium sulfate administration is the continuous IV regimen recommended by Zuspan, based on the proven clinical efficacy in the two largest magnesium sulfate trials The Zuspan regimen includes a loading dose of 4 g IV and maintenance dose of 1 g/hr IV and the posology of which has been confirmed effective by a number of studies through robust literature review. Many studies have shown intestinal magnesium absorption is balanced against renal magnesium excretion.

Magnesium deficiency in Hypomagnesaemia
Hypomagnesaemia is an electrolyte disturbance caused when there is a low level of serum magnesium (less than 1.46 mg/dL) in the blood. Hypomagnesaemia can be attributed to chronic disease, alcohol use disorder, gastrointestinal losses, renal losses, and other conditions. The magnitude of magnesium deficiency is said to be 1–2 mEq/kg of body weight. In general, mild hypomagnesaemia can be treated with oral supplements, whereas parenteral magnesium supplementation is required in more severe cases of hypomagnesaemia. Through a robust review of literature, there is evidence that IV supplementation is effective in normalising magnesium levels. The safe use of magnesium sulfate via IV administration is also evidenced through literature review.
Magnesium sulfate has been shown to cause exacerbation of selective symptoms, however, the benefit of magnesium sulfate therapy may outweigh the risks of exacerbation of the underlying condition.

Prevention and control of seizures in severe pre-eclampsia
NICE guidelines define pre-eclampsia hypertension presenting after 20 weeks, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or haematological complications. Severe pre-eclampsia is defined as having a blood pressure of >160 mmHg systolic or 110 mmHg diastolic, with worsening maternal organ dysfunction.

Clinically, magnesium sulfate has seen much attention within the obstetrics literature as an effective prophylactic and therapeutic agent for pre-eclampsia and eclampsia. For eclamptic seizure prophylaxis in pre-eclamptic women, magnesium sulfate has been shown to be superior to phenytoin, lytic cocktail (usually chlorpromazine, promethazine and pethidine) and diazepam, as well as causing fewer adverse effects. Overall observations through literature review supports the use of magnesium sulfate therapy for seizure prophylaxis in women with pre-eclampsia.

Prevention and control of recurrent seizures in eclampsia
Eclampsia is a medical emergency where high blood pressure results in seizures during pregnancy. Eclampsia is associated with cerebral oedema and cerebral vasospasm; and women with eclampsia may have cerebral oedema or cerebral ischaemia. Eclampsia is treated with anticonvulsant medication to control seizures and maintain a stable blood pressure with the goal of minimizing complications to both mother and baby. Magnesium sulfate is the standard therapy for prevention and treatment of eclampsia

Several randomised trials were reported comparing the efficacy of magnesium sulfate with other anticonvulsants in eclamptic women and magnesium sulfate was shown to have a superior effect in reducing the risk of recurrent seizures in eclamptic women, therefore, there is subsequent beneficial effects for the neonatal outcomes.

Post-marketing/Risk evaluation

There are other marketed formulations of magnesium sulfate, the MHRA Interactive Drug Analysis Profile includes all magnesium containing therapies in its report of Adverse Drug Reactions reported through the Yellow Card reporting scheme. Although the events incorporated all forms of magnesium and combination with other elements, a similarity was observed which coincided with the reported events in study reports. The most common events reported are flushing, nausea and vomiting, which are short term during initial administration. There are reports of irritation at the site of administration although this is reported more with the intramuscular route. Serious adverse events are rare and are generally related to hypermagnesemia and the associated toxicity. This risk can be reduced with careful dose titration and monitoring for early signs and symptoms of increased magnesium levels to avoid the serious adverse events of respiratory depression and cardiac arrest (*MHRA DAPS, 2020*).

MHRA conducted a safety review of the neonatal outcomes following maternal exposure to magnesium sulfate. This followed a review from the FDA in 2013 where magnesium sulfate is used in the treatment of tocolysis. There were 18 case reports identified skeletal abnormalities when administered to the mothers for tocolysis during pregnancy. Although there were no cases reported in the UK there is reports of electrolyte imbalance in neonates in literature and accumulation of magnesium in the neonatal blood is evident with longer administration to the mother. The safety review determined that prolonged or repeated use for longer than 5 days could result in decreased serum and urine neonatal calcium levels and increased magnesium neonatal serum levels. Therefore, this leads to the potential risk of skeletal developmental adverse effects including risk of fractures and osteopenia due to reduced osteogenesis process. (*MHRA Drug Safety update 2019*).

IV.6 Risk Management Plan (RMP)

The Applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

Considering the well-established physiological activity of magnesium sulfate in clinical settings and its well-established use in the treatment of hypomagnesaemia, severe pre-eclampsia and eclampsia, additional new clinical studies to those already available in the published literature were considered to be unnecessary.

The overall conclusion from the available clinical data is that appropriate treatment with magnesium sulfate has a favourable benefit risk balance. Its use in the intended populations, for the intended indications, at the intended therapeutic dose, is considered efficacious and well-tolerated when used in accordance with the recommendations proposed in the Summary of Product Characteristics, taking into account the overall safety profile of the drug and individual risk factors.

The 20% w/v solution offers a ready to use concentration suitable for intravenous administration avoiding the need to dilute the viscous higher strength (50% w/v) which is open to errors in dilution calculation and risking overdose which is associated with serious side effects and can be fatal. The vial sizes of 20 ml and 50 ml allow for ease of administration without the need for drawing from numerous vials leading to potential dosing errors.

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with magnesium sulfate heptahydrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**