Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Neomag 4mmol chewable tablets

(Magnesium glycerophosphate)

UK Licence Number: PL 36116/0003

Neoceuticals Limited

LAY SUMMARY

Neomag 4mmol chewable tablets
(magnesium glycerophosphate, chewable tablet, 4mmol)

This is a summary of the Public Assessment Report (PAR) for Neomag 4mmol chewable tablets (PL 36116/0003). It explains how Neomag 4mmol chewable tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Neomag 4mmol chewable tablets.

The product will be referred to as Neomag throughout the remainder of this public assessment report.

For practical information about using Neomag, patients should read the package leaflet or contact their doctor or pharmacist.

What is Neomag and what is it used for?
Neomag is a medicine with 'well established use'. This means that the medicinal use of the active substance, magnesium glycerophosphate, is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Neomag is given to supplement magnesium levels when the level of magnesium in the body is too low.

How does Neomag work?
Neomag contains magnesium in the form of magnesium glycerophosphate. Magnesium is an essential mineral which is important in many activities within the body, especially nerve and muscle function.

How is Neomag used?
The pharmaceutical form of this medicine is a chewable tablet and the route of administration is oral (by mouth).

The patient should always use this medicine exactly as their doctor has told them. The patient should check with their doctor or healthcare professional if they are not sure. The amount of Neomag the patient will be prescribed will depend on the patient's particular condition and needs.

Adults, including the elderly: The usual dose is 1-2 tablets three times a day. The patient's doctor may decide to monitor their magnesium levels at regular intervals.

Patients with poor kidney function may need to be monitored at regular intervals and dose adjusted.

Children: Neomag should only be used if a doctor has decided that the benefit of treatment outweighs any potential risk. Children need to be monitored regularly and have their dose adjusted.

- **Children below 4 years:** Not recommended as there is insufficient information regarding the use of Neomag tablets in this age group
- **Children (4 to 12 years):** 1 tablet twice per day
- **Children (12 to 18 years):** 1 tablet three times a day

Neomag tablets may be broken into quarters and chewed or swallowed with water.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Neomag have been shown in studies?
As magnesium glycerophosphate is a well-known substance, and its use as a magnesium supplement is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of magnesium glycerophosphate to supplement magnesium levels when the level of magnesium in the body is too low.

The Company also provided a bioavailability study for the active ingredient magnesium glycerophosphate. Bioavailability means the proportion of magnesium glycerophosphate which enters the circulation when introduced into the body and so is able to have an active effect.

What are the possible side effects of Neomag?
Like all medicines, Neomag can cause side effects, although not everybody gets them.

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Neomag approved?
The MHRA decided that the benefits of Neomag are greater than their risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Neomag?
A Risk Management Plan has been developed to ensure that Neomag is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Neomag, including the appropriate precautions to be followed by healthcare professionals and patients.

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

Other information about Neomag
A Marketing Authorisation for Neomag was granted on 10 January 2017.

The full PAR for Neomag follows this summary.

For more information about treatment with Neomag, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2017.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Neoceuticals Limited a Marketing Authorisation for the medicinal product Neomag (PL 36116/0003) on 10 January 2017. The product is a prescription only medicine (POM) indicated as an oral magnesium supplement for the treatment of patients with chronic magnesium loss or hypomagnesaemia as diagnosed by a doctor.

Neomag is also indicated for adult patients with hypomagnesaemia due to the concomitant administration of loop and thiazide diuretics or other drugs which cause hypomagnesaemia.

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

This application (PL 36116/0003) is a resubmission of an application made in 2010 for the same product. The previous application was refused on 19 October 2012 on clinical grounds following consideration of advice from the Commission on Human Medicines (CHM) that was provided to the MHRA in July 2011 and in September 2012 due to the applicant being unable to provide sufficient information to demonstrate the efficacy and safety of the product. The applicant submitted further evidence with their resubmission (PL 36116/0003) including a pharmacokinetic study (bioavailability study) which was referred to the Commission on Human Medicines (CHM) and Chemistry, Pharmacy and Standards Expert Advisory Group (CPS EAG) who met individually in November 2016 for consideration of whether the quality, efficacy and safety of the product was demonstrated. The applicant also updated their dossier in line with current regulatory requirements. Following consideration of the applicant's responses and further data that were submitted, the approval of the marketing authorisation was recommended.

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte. Magnesium is a factor in a number of enzyme systems, and is involved in neurochemical transmission and muscular excitability.

Supplements containing magnesium have been shown to be of use in restoring a magnesium deficit in humans. Given the central role that magnesium plays in human metabolism, magnesium replacement in the presence of a deficiency is an appropriate therapeutic action to take. This is particularly important given the significant clinical problems that can arise as a result of hypomagnesaemia in relation to the cardiovascular and neurological systems.

No new non-clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

Bibliographic data for the active substance magnesium glycerophosphate together with one clinical study (bioavailability study) have been submitted to support this application. The applicant has stated that the bioavailability study was conducted in accordance with good clinical practice (GCP) guidelines.

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

II QUALITY ASPECTS

II.1 Introduction

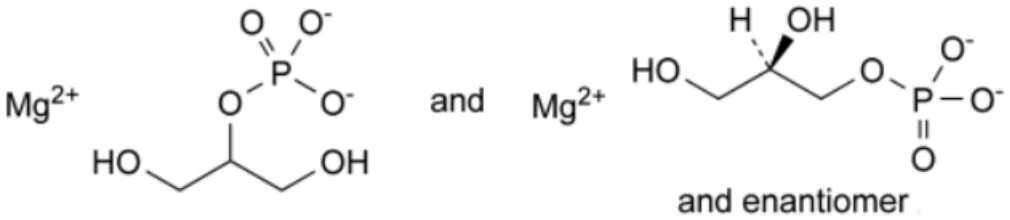
Each chewable tablet contains contains magnesium glycerophosphate equivalent to 4mmol (97mg) of magnesium. Other ingredients consist of the following pharmaceutical excipients maize starch, microcrystalline cellulose, talc, aspartame, magnesium stearate, colloidal anhydrous silica and povidone.

The finished product is packed into polypropylene plastic bottles with low density polypropylene (LDPE) / high density polypropylene (HDPE) blend caps containing 50 chewable tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN:	Magnesium glycerophosphate
Chemical name:	Mixture, in variable proportions, of magnesium salts of (*RS*)-2,3-dihydroxypropyl phosphate and 2-hydroxy-1-(hydroxymethyl)ethyl phosphate, which may be hydrated.

Structure:



Molecular formula:	$C_3H_7MgO_6P$
Molecular weight:	194.4 g/mol
Description:	White or almost white powder, hygroscopic
Solubility	Practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of acids.

Magnesium glycerophosphate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, chewable tablets containing magnesium glycerophosphate equivalent to 4mmol (97mg) of magnesium per tablet.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specifications

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened bottle with the storage conditions ‘Do not store above 25°C. Do not freeze. Store in the original packaging.’

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

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of magnesium glycerophosphate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

In accordance with the European Medicines Agency (EMA) guidance EMEA/CHMP/SWP/4447/000, Neomag is exempted from the need for an environmental risk assessment as the active substance, magnesium glycerophosphate, is an electrolyte. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

Neomag tablets have been supplied since September 2008 as a "Specials" product on a named-patient basis, supplied to hospitals and community pharmacies by Neoceuticals Limited (the Applicant).

There is evidence of an increasing requirement for oral magnesium glycerophosphate in the United Kingdom. During the period 2005-2008 approximately 15,000 "Specials" prescriptions were supplied in England by general practitioners and between October 2008 and December 2009 approximately 4800 prescriptions for the Applicant's product, Neomag tablets, were supplied to hospitals as a "special" across the UK.

Currently oral magnesium glycerophosphate is available on the General Sales List (List B) as a magnesium supplement, but not in the treatment of hypomagnesaemia. However the Applicant is proposing Neomag be a Prescription Only Medicine (POM) given the intended use.

Orally administered magnesium salts have been extensively used over many years and the Applicant has based this application on the well-established use principle of the active substance and has demonstrated the safety and efficacy of the product by referring to the published scientific literature, although a newly conducted bioavailability study is also included in the dossier.

The Applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

The legal basis, including the inclusion of new, non-bibliographic data as requested by CHM is appropriate.

Clinical background

Magnesium is the second most abundant intracellular cation after potassium, and the fourth most abundant cation of the body after calcium, potassium and sodium. Magnesium is involved in hundreds of enzymatic reactions and is essential for life. Magnesium is an important co-factor for many biological processes, most of which use adenosine triphosphate (ATP). Magnesium is an essential mineral that is important for bone mineralisation, muscular relaxation, neurotransmission and other cell functions. Magnesium deficiency has been reported in 20 to 60% of patients in intensive care units and around 12% of a general hospital inpatient population.

Magnesium deficiency produces a variety of clinical manifestations including positive Chvostek's and Trousseau's signs, seizures, muscle cramps, vertigo, nystagmus and psychiatric manifestations. In addition, cardiac arrhythmias such as supraventricular tachycardia and torsades-de-pointes may occur. Also, magnesium deficiency may be associated with hypokalaemia and hypocalcaemia.

In general, magnesium deficiency is the result of either gastrointestinal or renal magnesium losses. Common gastrointestinal causes of magnesium deficiency include any chronic diarrhoeal illness, intestinal malabsorption and steatorrhoea or as a consequence of intestinal bypass surgery. Acute pancreatitis can also be associated with hypomagnesaemia, similar to the observations of the association between pancreatitis and hypocalcaemia. Renal causes of hypomagnesaemia are either a primary defect in the tubular reabsorption of magnesium or disorders in which tubular sodium reabsorption is impaired. Thus, both loop and thiazide diuretics can inhibit magnesium reabsorption, although this effect is usually mild in clinical practice. Renal magnesium wasting is also found in alcoholic patients and seems to be due to alcohol-induced impairment of magnesium reabsorption. Several drugs have been associated with urinary magnesium wasting including aminoglycosides, amphotericin B, cisplatin, ciclosporin A and pentamidine. Renal magnesium wasting has also been associated with Gitelman syndrome and in some cases of Bartter syndrome. Renal magnesium wasting has also been noted as a result of antibody therapy targeting the EGF receptor. Other forms of renal magnesium wasting are associated with hypercalciuria, nephrolithiasis and nephrocalcinosis.

IV.2 Pharmacokinetics

Introduction and Overview

Magnesium is the main intracellular divalent cation, and under basal conditions the small intestine absorbs 30–50% of its intake. Normal serum magnesium ranges between 0.75–0.95 mmol/L at any age and approximately 20% of this is bound to albumin in the intravenous compartment. Even though 80% of serum magnesium is filtered at the glomerulus, only 3% of it is finally excreted in the urine. Altered magnesium balance can be found in diabetes mellitus, chronic renal failure, nephrolithiasis, osteoporosis, aplastic osteopathy and heart and vascular disease. Three physiopathological mechanisms can induce magnesium deficiency: reduced intestinal absorption, increased urinary losses, or intracellular shift of this cation. Intravenous or oral magnesium repletion is the main treatment for hypomagnesaemia, and potassium-sparing diuretics may also induce renal magnesium saving. Because the kidney has a very large capacity for magnesium excretion, hypermagnesaemia usually occurs in the setting of renal insufficiency and excessive magnesium intake.

Absorption and distribution

Normal magnesium body content is around 25g and 60–65% of it is located in the bone. Magnesium is the main intracellular divalent cation, 99% of it being in the intracellular space. The recommended magnesium dietary content for adults is approximately 250mg/day (62.5mmol/day) in men and 200mg/day (50mmol/day) in women.

Of the total amount ingested, approximately one third is eliminated in the urine and the remainder in the faeces. A small amount of magnesium (15 to 30 mg/day) is secreted into the gastrointestinal tract. Magnesium homeostasis involves the kidney, small bowel and bones.

In the gastrointestinal tract, magnesium absorption occurs primarily in the jejunum and ileum by both a passive paracellular mechanism and an active transport mechanism. However, most evidence suggests that magnesium is absorbed mainly by ionic diffusion and 'solvent drag' resulting from the bulk flow of water. It should be noted that the sigmoid colon has the capability to absorb magnesium and there have been reports in the literature of patients who developed magnesium toxicity after receiving enemas containing magnesium.

Under basal conditions the small intestine absorbs 30–50% of magnesium intake, although this percentage diminishes with increasing amount of magnesium intake, senescence and chronic renal disease. The magnesium absorptive process is, in part, under the influence of active vitamin D. Serum magnesium concentration correlates poorly with its body content, because patients with magnesium deficiency may have normal serum magnesium levels. The most reliable clinical method of evaluating its body content is the magnesium tolerance test.

In humans, less than 1% of total body magnesium is found in serum and red blood cells. It is distributed principally between bone (60-65%) and the intracellular compartments of muscle (20%) and soft tissues (20%). Ninety percent of this intracellular magnesium is bound to organic matrices.

Serum magnesium comprises only approximately 0.3% of total body magnesium, where it is present in three states—ionised (80%), protein bound (20%), mainly to albumin, and complexed to anions such as citrate and phosphate (5%). Equilibrium between tissue pools is reached slowly with a half-life for the majority of radiolabelled magnesium varying between 41 and 181 days. Thus, magnesium estimations from blood may not provide representative information on the status of other magnesium stores.

Metabolism
Three physiopathological mechanisms can induce magnesium deficiency: reduced magnesium intestinal absorption (e.g. malabsorption), increased urinary magnesium losses (e.g. diuretics), or intracellular shift of magnesium (e.g. hungry bone syndrome).

Even though, during nutritional deficiency states, the intestine is able to increase its absorptive capability by as much as 40% compared with normal, malnutrition can lead to magnesium deficit, especially in the setting of chronic alcoholism. Enteric diseases which induce malabsorption (e.g. inflammatory bowel disease) may also cause magnesium deficiency related to the digestive tract. Renal magnesium wasting may appear in the setting of volume expansion, osmotic diuresis (e.g. glycosuria, post-obstructive diuresis), treatment with diuretics (loop diuretics and thiazide but not potassium-sparing diuretics), phosphorus depletion, tubular damage induced by drugs (cisplatin, amphotericin, aminoglycosides), or renal diseases (interstitial nephritis, Fanconi syndrome, Gitelman syndrome, etc.).

Calcineurin inhibitors (ciclosporin and tacrolimus) also increase renal loss of magnesium and the subsequent hypomagnesaemia enhances nephrotoxicity due to calcineurin inhibitors. A high serum ionised calcium level is another mechanism of magnesium urinary wasting, because of direct stimulation of the basilar calcium sensor of the loop of Henle.

Low serum magnesium secondary to its shift into the intracellular compartment only acquires clinical significance in re-feeding or hungry bone syndromes. Hypomagnesaemia can, by itself, induce hypokalaemia (often refractory to potassium repletion until magnesium deficit is corrected), neuromuscular irritability, tetany, seizures, depression, carbohydrate intolerance, hypocalcaemia,

digoxin cardiotoxicity, and tachyarrhythmias resistant to standard therapy, and they respond only to magnesium repletion. For this reason, in clinical conditions such as pre-eclampsia, acute myocardial infarction, tachycardia, torsade-de-pointes, etc., intravenous magnesium treatment is advocated.

Acute intravenous magnesium infusion can induce a reduction of its absorption in the thick ascending loop of Henle, and, consequently, a considerable amount of the administered magnesium will be excreted in the urine. For this reason oral administration in asymptomatic patients is the preferred method of administration for magnesium repletion.

The Applicant has provided a full discussion of the pharmacokinetics of magnesium and factors affecting absorption, distribution and handling. This is considered sufficient for this application.

Excretion
The major excretory pathway for absorbed magnesium is through the kidney. The renal excretion of magnesium is about 120 to 140mg/24 hours for an adult on a normal diet. Thus the amount of magnesium absorbed from the small intestine is similar to the amount excreted by the kidney for a person in normal magnesium balance. Indeed the kidney is the major organ that controls the magnesium concentration in the serum. Thus the kidney plays a crucial role in the maintenance of magnesium balance, with approximately 2g of magnesium being filtered by the kidney of which about 100mg appears in the urine. Therefore, even though 80% of serum magnesium is filtered at the glomerulus, only 3% of it is finally excreted in the urine. Renal excretion is determined largely by the rate of filtration and its tubular re-absorption, while tubular secretion does not seem to play a significant role in its renal handling. Between 10 and 15% of filtered magnesium is re-absorbed in the proximal convoluted tubules, while 60–70% is passively reabsorbed in the thick ascending loop of Henle. In the distal convoluted tubules, magnesium re-absorption is still significant and represents the fine regulation of its excretion. Among the main stimuli that increase the urinary magnesium excretions are: high natriuresis, osmotic load, and metabolic acidosis. Among those that reduce it are: metabolic alkalosis, parathyroid hormone, and possibly, calcitonin.

The ageing process does not modify the fractional excretion of magnesium (FEM) in healthy individuals, but if these people undergo a volume overload their FEM increases to a point that significantly lowers their serum magnesium level. Because it has been shown that sodium re-absorption is reduced in the thick ascending loop of Henle in healthy old people, and this tubular segment is the main one implicated in magnesium re-absorption, it could be hypothesised that this phenomenon could explain the increased fractional excretion of magnesium that elderly people have when they are volume expanded.

The average magnesium oral intake of a normal adult is approximately 12mmol/day. In addition to this, approximately 2mmol/day of magnesium is secreted into the intestinal tract in the bile and pancreatic and intestinal juices. From this average total amount that is presented to the intestine on a daily basis (14mmol) about 6mmol (30%) is absorbed giving a net absorption of about 4mmol/day. The remaining 8mmol is excreted in the faeces.

Assessor's overall conclusions on pharmacokinetics
The pharmacokinetics of this drug has been adequately discussed.

Bioequivalence
The following bioavailability study has been conducted in support of this bibliographic application:

STUDY

An open label, randomised, single dose, two treatment, two period, two-way, crossover comparative study to determine the bioavailability of the test product Neomag 4mmol chewable tablets (Neoceuticals Ltd, UK) versus the reference product Magnesium Sulphate IV Injection 10% (Martindale Pharmaceuticals Ltd, UK) after administration to healthy adults under fasting conditions.

Subjects were administered a single dose either orally (2 tablets of the **test product** containing 194.4 mg (8mmol) magnesium in total) or intraveneously as a single infusion (a single intravenous dose of 10 ml of the **reference product** containing 4 mmol (97.2 mg) magnesium) under fasting conditions.

Urinary excretion of magnesium was measured after administration of the drugs for up to 48 hours. Pre-dose urine volumes were not recorded meaning baseline magnesium excretion could not be calculated. The washout period between the treatment phases was 3 days. The pharmacokinetic results are presented below:

Table: Summary of ANOVA on Ae_{adj} following a single oral dose of Neomag (Test) and Magnesium Sulphate IV injection (Reference) to healthy subjects:

	LS Geometric Mean		Test as Percentage of Reference		
Parameter	Test	Reference	Estimate	90% CI	P-Value
Ae_{adj}	0.792	2.14	37.1	(34.3, 40.2)	<0.001*

LS = Least squares

CI = Confidence Interval

Aeadj: The total amount of magnesium excreted in the urine, adjusted for the total dose administered (i. e. Ae/dose).

Table: Sensitivity analysis: Summary of ANOVA on Ae_{adj} following a single oral dose of Neomag (Test) and Magnesium Sulphate IV injection (Reference) to heathy subjects after adjusting for baseline amounts of magnesium:

Assumed Reference	Test Ae_{adj}	Reference	Test as Percentage of Reference	
Recovery	LS Mean	Assumed	Estimate	90% CI
100%	0.238	1.0	23.8	(17.4, 30.3)
90%	0.198	0.9	21.9	(15.5, 28.4)

LS = Least squares

CI = Confidence Interval

The conclusions from this bioavailability study are:

- The recovery of magnesium in urine following oral (Neomag) compared to that following intravenous infusion of magnesium showed that magnesium was absorbed after an oral dose of Neomag.
- The average amount of magnesium excreted in urine following oral administration of Neomag was estimated to be 37.1% (90% CI 34.3% to 40.2%) of the levels of magnesium excreted following administration of the magnesium sulphate IV injection (based on dose adjusted values). However, care should be taken when interpreting this result as an estimate of absolute bioavailability since amounts were not adjusted for baseline levels.
- Assuming there was 100% recovery of the reference formulation, the absolute bioavailability of Neomag (based on baseline adjusted Ae_{adj}) was estimated to be 23.8% (90% CI: 17.4% to 30.3%). Under this assumption the dose of Neomag would need to be increased by 4.2-fold to achieve similar levels of exposure seen following an equal IV dose of magnesium sulphate.

- When only 90% recovery of the reference formulation is assumed, the estimated absolute bioavailability of Neomag falls to approximately 21.9% (90% CI: 15.5% to 28.4%).
- An absolute oral bioavailability of Neomag in the present study (21.9% to 23.8%) was within the range of bioavailability for other formulations of oral magnesium (19% to 45%).

Assessor's conclusion on bioavailability
It is agreed that the bioavailability study does supply information on the bioavailability of Neomag in healthy volunteers. Although serum concentrations were not measured, the rationale behind this is understood and accepted and urinary data is considered an acceptable surrogate. The failure to measure baseline urine volumes has been adequately accounted for.

To consider if the bioavailability results obtained for Neomag in healthy volunteers are translatable to hypomagnesaemic patients it is appropriate to compare the absorption, distribution, metabolism and elimination (ADME) characteristics of magnesium following the administration of the product in these two situations. In relation to absorption it should be noted that the intestinal absorption of magnesium is not directly proportional to the actual amount of the oral magnesium administered, rather it is dependent upon the overall magnesium states of the individual concerned. This is the same whether the individual is a normal healthy volunteer or a patient with hypomagnesaemia. In both healthy volunteers and patients, the lower the total body magnesium levels, the more magnesium is absorbed through the gut and vice versa. This is the driving factor in relation to magnesium if the small intestine is affected by a gastrointestinal disease, such as Crohn's. However, in this situation, if the patient did have such a concomitant disease then it would be inappropriate to give them oral magnesium supplements.

Following the absorption of magnesium, distribution would then occur. The distribution of magnesium in humans is known to be extensive with a large proportion located in bone. There are no reasons to expect that the distribution of magnesium would be any different in human volunteers or patients. In relation to metabolism, the magnesium ion is neither metabolised nor undergoes biotransformation, again this is the same in volunteers and patients. Finally, magnesium is excreted unchanged via the kidneys. The excretion of magnesium is reduced in the presence of severe renal failure (GFR<30ml/min) as might be the case in some patients. This fact is well established and although in this situation it is advised that oral magnesium supplements are not administered to such patients, this would have no effect on the actual bioavailability of magnesium from Neomag.

Therefore, the only factor that would affect the bioavailability of magnesium from Neomag would be the presence of disease of the small intestine, otherwise the bioavailability would be the same in both human volunteers and patients. In conclusion, having considered the ADME characteristics of magnesium following the administration of the product, the results obtained from the bioavailability study in volunteers are translatable to hypomagnesaemic patients.

The Applicant has addressed the consideration of translating the bioavailability results obtained for Neomag in healthy volunteers to hypomagnesaemic patients satisfactorily.

It would be advisable to measure at least periodically blood concentrations of magnesium especially in patients at risk and the Applicant has included the following relevant statement in the SmPC:
'It is recommended that serum magnesium levels should be monitored at regular intervals (e.g. every 3-6 months), particularly in children and in patients with renal impairment.'
This is satisfactory.

IV.3 Pharmacodynamics
Magnesium is the fourth most common cation in the body and the second most common intracellular cation after potassium. It has a fundamental role as a co-factor in more than 300 enzymatic reactions

involving energy metabolism and nucleic acid synthesis. It is also involved in several processes including hormone receptor binding, gating of calcium channels, transmembrane ion flux and regulation of adenylate cyclase, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability and neurotransmitter release. In many of its actions it has been likened to a physiological calcium antagonist.

Magnesium units are commonly expressed in magnesium mmol or mEq. Neomag chewable tablets contain 925 mg of magnesium glycerophosphate, which is equivalent to 4 mmol, 8 mEq or 97 mg of elemental magnesium. While there is an absolute requirement for magnesium, the daily estimated average requirement (EAR) is 200mg (50mmol) for adult females and 250mg (62.5mmol) for adult males. The actual amounts required are smaller in infants and children but are increased during pregnancy. Rich sources of magnesium in the diet include cereals and legumes, but the processing of the former may lead to marked depletion of inherent magnesium, leaving only 3–28% of the original content.

Magnesium absorption is inversely proportional to intake and occurs principally from the jejunum, ileum and colon. Excretion and serum magnesium control occur via the kidney. In common with other cations, magnesium is filtered at the glomerulus, but differs in that re-absorption is predominantly in the ascending limb of the loop of Henle and not in the proximal convoluted tubule.

Assessment of magnesium status is a complex area. Older methods such as serum magnesium estimation are criticised because only 0.3% of total body magnesium is found in serum. Moreover, the sample could be affected by magnesium from red blood cells, which have three times the magnesium concentration of serum, should haemolysis occur. Urinary magnesium estimates throughput of magnesium, but does not focus on total body assessment. However, serum total magnesium is used commonly and has a place in the acute situation or for monitoring levels during therapy. Normal concentrations are debated, but taking a mean concentration of 0.860 mmol/L, and assuming normal distribution, a typical reference range of 0.75–0.95mmol/L can be calculated.

Another approach for assessment of magnesium status is urinary magnesium excretion. A 24-h estimation is of principal use in identifying aberrant renal excretion with a normal daily urinary loss of 3.6mmol for females and 4.8mmol for males. A further refinement is the magnesium tolerance test. After a baseline 24-h urine collection, a parenteral load of magnesium is administered and a further 24-h urine collection obtained. Although there is no standardisation of the test, excretion of greater than 60–70% of the magnesium load suggests that magnesium depletion is unlikely. This test principally quantifies the major exchangeable pool of magnesium, such as bone.

The development of Neomag chewable tablets has been focused on providing oral magnesium supplementation in hypomagnesaemia and not as a basis for pharmacological therapy. Primary and secondary magnesium deficiencies constitute the sole indication of physiological oral magnesium supplementation therapy. It is therefore necessary to be well acquainted with the clinical pattern of magnesium deficit and to discriminate between magnesium deficiency due to an insufficient magnesium intake which only requires oral physiological supplementation and magnesium depletion related to a dysregulation of the control mechanisms of magnesium status.

Physiological oral magnesium load constitutes the best tool for diagnosis of magnesium deficiency and the first step of its treatment. Physiological oral magnesium supplementation (approximately 12mmols/day) is easy and can be carried out in the diet or with magnesium salts, with practically only one contraindication namely, overt renal failure. In order to use the pharmacological properties of induced therapeutic hypermagnesaemia, high oral doses of magnesium (> 24mmols/day) are advisable for chronic indications and the parenteral route is suitable for acute indications.

Pharmacological magnesium therapy is mainly focused on obstetric and cardiological conditions. The main indications are eclampsia, some dysrhythmias (torsade de pointe particularly) and myocardial ischaemia, which utilise predominantly the intravenous route of administration of magnesium. Physicians should be familiar with the numerous conditions and therapeutics that are risk factors for an underlying magnesium deficiency and in which empiric magnesium replacement should be considered.

Reference levels for magnesium in plasma are typically cited between the range of 0.75-0.95mmol/L**.** Symptoms of magnesium deficiency, that is a plasma level of less than 0.5mmol/L, should be treated empirically and the dose adjusted according to response and tolerance.

The pharmacodynamics of magnesium are explained in the Applicant's original dossier submission and are considered sufficient.

Assessor's overall conclusions on pharmacodynamics
There is no information on pharmacodynamics included in the addendum to the clinical overview. Referring to the original clinical overview from 2010 (not resubmitted) the pharmacodynamics are acceptably explained. There is scant explanation as to how the dynamics of magnesium extrapolate to the selected poslogy, however it is accepted that dose will be primarily determined by clinician discretion and based upon available serum magnesium levels as a surrogate marker for total body stores. This is deemed acceptable.

IV.4 Clinical efficacy

Neomag has been developed as a treatment for physiological hypomagnesaemia and not as a pharmacological therapy in the treatment of pathological states, namely cardiological or obstetric disorders.

As the Applicant has stated, this marketing authorisation application is concerned at the licensing of Neomag in the restoration of hypomagnesaemia to within normal physiological limits. The efficacy of a supplement to replace a mineral deficiency is reflected by the ability of that supplement to adequately restore the deficit and maintain physiological levels. Adequate bibliographical references have been presented by the Applicant which demonstrate that oral supplements containing magnesium are of use in restoring that deficit.

In the addendum to the clinical overview supplied as the integral part of this dossier there have purportedly been three new pieces of evidence which have been included as fundamental to the Applicant's submission.

1. Retrospective observational clinical audit
2. Randomised clinical study of IV vs oral magnesium supplementation in cisplatin-induced hypomagnesaemia.
3. Anecdotal and case reports in the literature of treatment of hypomagnesaemia with orally administered magnesium glycerophosphate

Retrospective Observational Clinical Audit:
For this clinical audit, 40 inpatients were identified from the pharmacy records from different hospital establishments. These 40 patients (21 male and 19 female) had a mean age of 62.6 (range 20-94 years) and had concomitant diseases that included gastritis, duodenitis, diverticulitis, coeliac disease, Crohn's disease, alcoholism, diabetes, cardiac disease, liver disease and cancer. Baseline and at least one post treatment laboratory determination of serum magnesium was made in 38 patients with between 2 and 6 samples taken between 0 and 18 days. From these 38 patients, the baseline mean serum magnesium concentration was 0.64mmol/L (0.34 – 0.80mmol/L range). Patients received a variety of dosage

regimens of magnesium glycerophosphate tablets between 8mmol and 24mmol per day, as per BNF recommendations.

Of the 37 patients who had baseline magnesium levels recorded, 11 (29.73%) had recorded serum magnesium concentrations of 0.7mmol/L or above and consequently did not warrant magnesium supplementation as per the posology of the SmPC for Neomag.

Of the 26 patients who received Neomag in line with the product's SmPC 10 (38.46%) failed to achieve a magnesium concentration greater than or equal to 0.7mmol/L after a treatment period ranging between 2 and 18 days and a Neomag dose of between 16 and 24mmol per day. In two patients there were significant isolated spikes in the serum concentration of magnesium to >1.0mmol/L (patient 2 and patient 35) suggesting either spurious laboratory resulting, or parenteral administration of magnesium which was predefined as an exclusion criteria to the audit. In patient 2 the serum magnesium concentration fell again to below normal levels by the end of the follow up period (18 days) despite ongoing administration of 24mmol/day of Neomag. In patient 35, the initial serum concentration was greater than 0.7mmol/L of magnesium meaning this patient received Neomag outside of the posology of the SmPC for Neomag, but despite this and an unexplained spike in serum magnesium concentration on day 5, the serum magnesium concentration at the end of the follow up period (day 10) was lower than on commencing therapy with 24mmol/day of Neomag.

From this data it is difficult to determine evidential value given that the numbers of participants involved are very small and there is no provision made for controlling for selection bias in particular. In some individual patients, serum magnesium levels fell and a large proportion of patients failed to achieve normalisation of serum magnesaemia despite prolonged treatment with maximal dose Neomag (in accordance with the SmPC). However, the data do show that there does tend to be an increase in overall serum magnesium levels in patients treated with varying doses of magnesium glycerophosphate, trending towards a normalisation in serum magnesium levels.

The regression coefficient of the slope has been calculated and the extrapolation of the equation suggests that normalisation of serum magnesium could be expected if treatment had been continued until day 14 in those in whom the follow up period did not reach this point. In 6 patients who did receive supplementation until beyond day 14, 4 of these (66.66%) achieved a normalisation of serum magnesium levels within this time period. Without full details of the patients included it is difficult to determine the cause for treatment failures in those who did not achieve a normomagnesaemia in this interval.

In summary, this audit data supplies limited evidence for the efficacy of magnesium glycerophosphate tablets in treating hypomagnesaemia, although this is sufficient for authorisation.

Randomised clinical study of IV vs oral magnesium supplementation in cisplatin-induced hypomagnesaemia:
This study was already included in the previous application in 2011. This study includes 41 magnesium replete patients who were due to begin treatment with the cytotoxic agent cisplatin which is known to cause renal magnesium loss. The patients were randomised to intravenous magnesium sulphate, oral magnesium pidolate (2g or 7.15mmol, three times daily on days 2 to 21 of each cisplatin course) or no treatment. The mean serum magnesium levels after the fourth course of chemotherapy were 1.47, 1.79 and 1.85mg/dL for control group, intravenous and oral therapy respectively. Three of nine (33%) of the intravenous group and four of nine (44%) of the oral supplement group developed hypomagnesaemia after the fourth cisplatin cycle compared to nine out of ten (90%) of the control group.

This study is of limited value due to its small size, the lack of normality to the magnesium levels' distribution and absence of confidence intervals. However, there is some evidence that oral magnesium

supplementation can have some effect in preventing hypomagnesaemia in patients treated with cisplatin. This article may be deemed supportive.

Anecdotal and case reports in the literature of treatment of hypomagnesaemia with orally administered magnesium glycerophosphate:
Again, these same bibliographic references were supplied as evidence in the previous application for this product. On the previous application these case reports were deemed scant evidence for the efficacy of oral magnesium glycerophosphate.

In a study, a series of 16 patients received ESHAP chemotherapy for relapsed lymphoma. Magnesium supplementation was administered if pre-treatment levels were less than 0.7mmol/L. Mean serum magnesium levels prior to each cycle showed a sequential reduction with an associated increase in the amount of magnesium supplementation required. Magnesium was administered in 12 of 21 episodes of hypomagnesaemia, mainly as intravenous magnesium sulphate. It is not clear from the case series how many patients actually received oral magnesium glycerophosphate, or what the outcome was.

In another study, a series of 10 patients on long term proton pump inhibitor (PPI) therapy with severe hypomagnesaemia; eight patients also were receiving diuretics. Four patients received 12-24mmol/day oral magnesium glycerophosphate while all patients received intravenous magnesium. The authors conclude that oral magnesium supplements were only partially effective at treating hypomagnesaemia whilst the PPI therapy was ongoing. Hypomagnesaemia was only resolved when PPI therapy was discontinued.

In a recorded case of a single magnesium deficient patient on omeprazole who was treated with intravenous magnesium followed by oral magnesium glycerophosphate of an unrecorded dose and duration, after discontinuing the PPI, the serum magnesium had normalised within six weeks.

Two reported cases of PPI induced hypomagnesaemia: In both of these cases the magnesium normalised upon stopping the PPI but the effect of oral magnesium therapy is not clear.

Another case discusses a patient with PPI induced hypomagnesaemia who failed to respond to oral magnesium therapy (24mmol/day) and whose magnesium levels were only normalised by stopping the offending PPI.

A further report on a small case series of four patients with hypomagnesaemia secondary to short bowel syndrome who received fortnightly IV magnesium and 12mmol/day oral magnesium glycerophosphate to keep plasma magnesium levels above 0.5mmol/L. Plasma magnesium levels in all four increased when this regime was substituted for magnesium-L-aspartate (30-50mmol/day).

Another case demonstrates a patient with hypomagnesaemia due to short bowel syndrome who failed to respond to oral magnesium glycerophosphate of up to 108mmol/day but did show a response to oral magnesium oxide (67.5mmol/day).

The above referenced individual cases provide some supportive evidence of the efficacy of magnesium glycerophosphate in treating hypomagnesaemia.

Assessors' overall conclusions on clinical efficacy
The evidence presented in support of the Applicant's product in the proposed indication of treating hypomagnesaemia is scant. However, it is recognised that the available repository of published literature in the use of oral magnesium supplementation is limited. The data that is provided may be considered supportive to a marketing authorisation and when assessed in aggregate with the literature provided in the original application and with the results of the clinical audit, is considered sufficient to concur with the Applicant's position on efficacy of Neomag tablets in the proposed indication.

IV.5 Clinical safety

Introduction
Clinical safety of magnesium glycerophosphate was raised by the CHM and was addressed by the Applicant.

As previously, the studies cited provide only limited safety data from fewer than 100 subjects in clinical trials. One author investigated the effects of 6 weeks of therapy with oral enteric coated magnesium chloride (15.8mmol magnesium /day) in 21 patients with congestive cardiac failure. Gastrointestinal adverse effects were reported by 8 patients, necessitating withdrawal in 2 cases. Another author examined the effects of oral magnesium oxide (476mg elemental magnesium per day) for 8 weeks on the lipid profile of 50 healthy volunteers. Over a third of subjects experienced diarrhoea which led to the withdrawal of 6 subjects. A study investigated the effects of short term oral enteric coated magnesium chloride therapy as a tocolytic agent in 25 women with 5 reports of gastrointestinal side effects reported.

The EC Scientific Committee on Food report on the tolerable upper intake level of magnesium (2001) concludes easily dissociable magnesium salts exhibit dose dependent laxative effects and that mild diarrhoea occurs in a small percentage of adults at oral doses of above 360mg/day. This is reversible on cessation of therapy. The opinion of the Committee was that toxic hypermagnesaemia is only seen at oral magnesium doses greater than 2500mg. Advanced age does not seem to be a risk factor for toxicity since in one study, 64 geriatric patients with a mean age of 81 years receiving a daily dose of 28mmol magnesium hydroxide (approximately 680mg magnesium), did not develop hypermagnesaemia.

Post marketing surveillance of oral magnesium products over several decades has not revealed any particular safety concerns.

The safety of the product is deemed to be acceptable on these grounds.

Assessor's overall conclusions on clinical safety
Overall the safety of the product at the proposed dose levels is acceptable.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system

The marketing authorisation holder (MAH) has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Neomag.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns as approved in the RMP:

Summary of safety concerns	
Important identified risks	• Use in patients with renal dysfunction • Reduced magnesium absorption in patients with congenital short bowel syndrome and those who have undergone extensive bowel resection • Drug interactions
Important potential risks	• None
Missing information	• Use in pregnancy • Paediatric use

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

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

V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use.*

VI Overall conclusion, benefit/risk assessment and recommendation

Orally administered magnesium salts have been extensively used over many years. The Applicant has based the current application on the well-established use principle of the active substance and has demonstrated the safety and efficacy of the product by referring to the published scientific literature. A newly conducted bioavailability study is also included in the dossier.

It is recognised that the available repository of published literature in the use of oral magnesium glycerophosphate preparations is limited. However, the data that are provided may be considered sufficient to support a marketing authorisation when assessed in aggregate with the literature provided in the original application together with the results of the new empirical pharmacokinetic study data and the clinical audit.

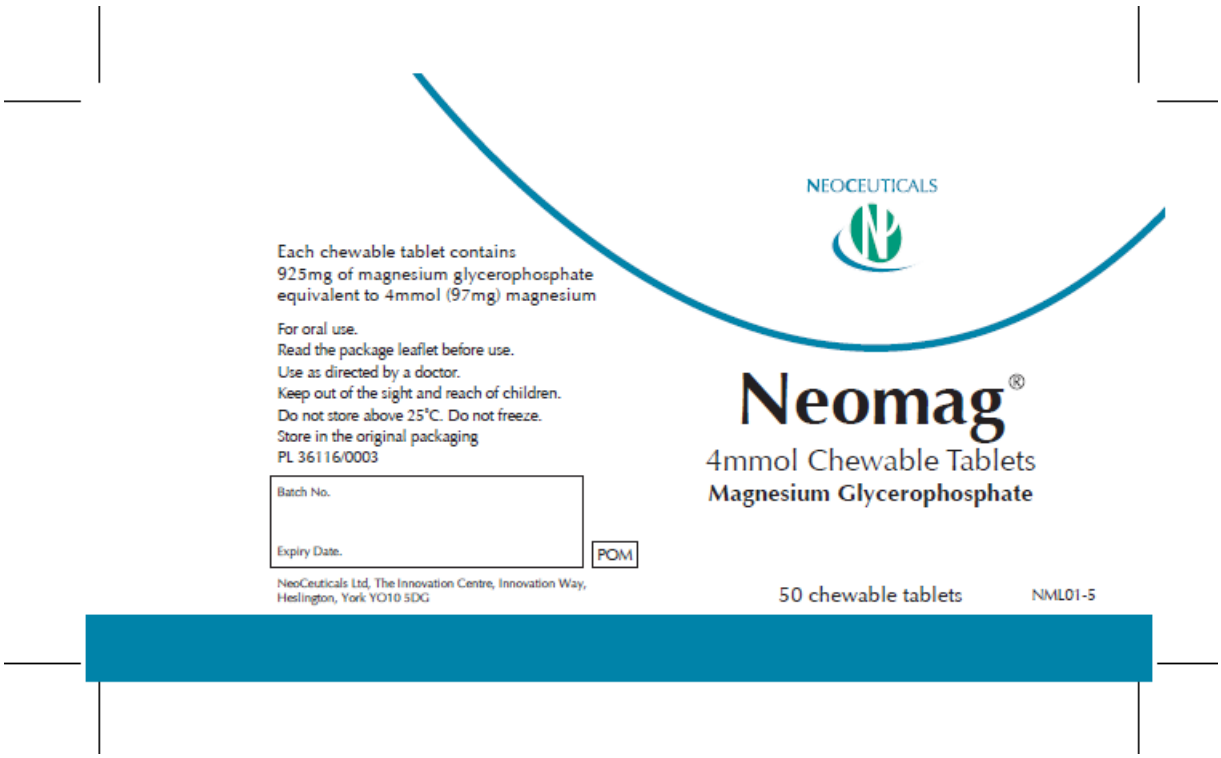
The application complies with CHMP guidance documents and there are no indications in the light of scientific knowledge that it differs significantly from the other similar medicinal products with regard to safety or efficacy. The product contains the widely used and well-known active substance magnesium which has a long history of established favourable risk-benefit profile.

In conclusion, the application may be considered approvable.

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

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:


NEOCEUTICALS
Each chewable tablet contains
925mg of magnesium glycerophosphate
equivalent to 4mmol (97mg) magnesium
For oral use.
Read the package leaflet before use.
Use as directed by a doctor.
Keep out of the sight and reach of children.
Do not store above 25°C. Do not freeze.
Store in the original packaging
PL 36116/0003
Batch No.
Expiry Date.
POM
NeoCeuticals Ltd, The Innovation Centre, Innovation Way,
Heslington, York YO10 5DG
Neomag®
4mmol Chewable Tablets
Magnesium Glycerophosphate
50 chewable tablets
NML01-5

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**