Magnesium Diasporal 400 mg direkt

Granules

Active substances: magnesium citrate and magnesium oxide

EU-Risk Management Plan

December 2015

Active substance(s) (INN or common name):	magnesium citrate, magnesium oxide
Pharmaco-therapeutic group (ATC Code):	A12CC30
Name of Marketing Authorisation Holder or Applicant:	Protina Pharmazeutische Gesellschaft mbH Adalperostraße 37 85737 Ismaning Germany
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Magnesium Diasporal direkt 400 mg

Data lock point for this RMP	12/2015	Version number: 1.1
Date of final sign off	depending on approval date	

PART I: PRODUCT OVERVIEW

Administrative information on the RMP

Part	Module/Annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	Depending on approval date	NA
	SII Non-clinical part of the safety specification	Depending on approval date	NA
	SIII Clinical trial exposure	Depending on approval date	NA
	SIV Populations not studied in clinical trials	Depending on approval date	NA
	SIV Populations not studied in clinical trials	Depending on approval date	NA
	SVI Additional EU requirements for the safety specification	Depending on approval date	NA
	SVII Identified and potential risks	Depending on approval date	NA
	SVIII Summary of the safety concerns	Depending on approval date	NA

Part III Pharmacovigilance Plan		Depending on approval date	NA
Part IV Plan for post-authorisation efficacy studies		Depending on approval date	NA
Part V Risk Minimisation Measures		Depending on approval date	NA
Part VI Summary of RMP		Depending on approval date	NA
Part VII	A N N E X 2	Depending on approval date	NA
Annexes	Current or proposed SmPC/PIL	Depending on approval date	NA
	ANNEX 3 Worldwide marketing status by country	Depending on approval date	NA
	ANNEX 4 Synopsis of clinical trial programme	Depending on approval date	NA
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Depending on approval date	NA
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Depending on approval date	NA
	ANNEX 7 Specific adverse event follow-up forms	Depending on approval date	NA
	ANNEX 8 Protocols for studies in Part IV	Depending on approval date	NA
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Depending on approval date	NA

	ANNEX 10 Details of proposed additional risk minimisation activities	Depending on approval date	NA
	ANNEX 11 Mock up examples	Depending on approval date	NA
	ANNEX 12 Other supporting data	Depending on approval date	NA

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Overview of versions

Version number of last agreed RMP

Not applicable. This is the first RMP of the product.

Current RMP versions under evaluation

Not applicable. This is the first RMP of the product.

PRODUCT DETAILS	
Invented names in the European Economic Area (EEA)	Magnesium Diasporal direkt 400 mg
Authorisation procedure	DCP

Brief description of product (chemical class, mode action etc.)	Magnesium Diasporal 400 mg direkt Granules belongs to the pharmacotherapeutic group "mineral supplements" (ATC Code A12CC30). One sachet (2.22 g) contains magnesium hydrogencitrate 647.06 mg and magnesium oxide 572.10 mg corresponding to 400 mg magnesium. Both active ingredients are in well-established use as lozenges or capsules in the EU as they have been authorised and marketed in Austria and Germany for far more than ten years.
Indication(s) in the EEA	Treatment and prevention of magnesium deficiency
Posology and route of administration in the EEA	Posology 1 sachet of granules daily (400 mg magnesium). Method of administration For oral use. Magnesium Diasporal direkt 400 mg granules should be taken directly into the mouth onto the tongue and swallowed without water shortly before a meal.
Pharmaceutical form and strength(s)	Pharmaceutical form: granules Strength: 400 mg

Country and date of first authorisation worldwide	NA
Country and date of first launche worldwide	NA
Country and date of first authorisation in the EEA	NA
Is the product subject to additional monitoring in the EU?	no

PART II: MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication

Brand names of concerned products (with this indication)

SI.1 Epidemiology of the disease

Magnesium Diasporal 400 mg direkt is intended to treat and prevent magnesium deficiency. Hypomagnesaemia is a quite unspecific pathological phenomenon potentially triggered by a variety of underlying conditions; therefore the epidemiologic characterisation of the indication and the target population is difficult.

Indication/target population	**Magnesium deficiency**
Incidence and prevalence of target indication	The prevalence of hypomagnesaemia in the general German population ranges from 2.5-15% (Schimatschek and Rempis 2001), and it might be higher in special patient populations.
Mortality in target indication	Abnormalities of magnesium levels can result in disturbances in nearly every organ system and can cause potentially fatal complications, including amongst others ventricular arrhythmia or coronary artery vasospasm (Connor 2011).
Potential health risk	Risk of mortality
Demographic profile of target population	Magnesium Diasporal 400 mg direkt is indicated in adults. The safety and efficacy of Magnesium Diasporal 400 mg direkt in children has not been established.

During recent years, several large epidemiological studies have been published suggesting a risk reducing effect of a high magnesium intake and /or a low plasma magnesium concentration with regard to various diseases or an increased risk with low intake.

In epidemiological studies, an inverse correlation between magnesium intake and the risk of developing diabetes mellitus (T2DM) was found (Kao et al., 1999; Lopez-Ridaura et al., 2004, Song et al., 2006). The WHS enrolled a cohort of 39345 US women aged at least 45 years. During a follow-up period of 6 years, on average, 918 women developed T2DM. The trial results support a protective role for higher magnesium intake and a reduced risk of developing T2DM, in particular in the subgroup of overweight women (Song et al., 2006). In two other large prospective studies, the Nurses' Health Study (NHS) initiated in 1976 and the Health

Professionals Follow-up Study (HPFS), which began in 1986, an inverse correlation between magnesium intake and the risk of developing T2DM was observed for women as well as for men (Lopez-Ridaura et al., 2004). The investigators examined the association between magnesium intake and risk of T2DM in 85060 women and 42872 men without any previous history of diabetes, cardiovascular disease or cancer at baseline. After 18 years follow-up, 4085 cases of T2DM were documented in women, and after 12 years follow-up, 1333 T2DM cases were found in men. When comparing the highest and lowest magnesium consumption, the relative risk for T2DM was in the highest-magnesium group 0.66 in women, (95% CI 0.60-0.73, $P < 0.001$) and 0.67 in men (95% CI 0.56-0.80, $P < 0.001$) (Lopez-Ridaura et al., 2004). Furthermore, in the Atherosclerosis Risk in Communities Study (ARIC), a low serum magnesium level was found to be a strong independent predictor of incident T2DM among middle-aged white participants (Kao et al., 1999). Findings from large observational studies, carried out in various other regions in the world, have had similar results. For instance, in a large, population-based prospective study including 64191 middle-aged Chinese women, a non-linear inverse association between calcium and magnesium consumption and the incidence of T2DM was observed after 7 years follow-up. Future controlled studies must, however, investigate whether the intake of these elements is protective for the development of T2DM in this population (Villegas et al., 2009). Moreover, it was noted in an assessment of 1453 adults in Australia that hypomagnesaemia was on average 8.6 times more common in patients with diabetes and 10.5-fold higher in newly diagnosed diabetics than in healthy individuals (Simmons et al., 2009). In the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam Study, which included 9702 men and 15365 women, dietary intake of fiber and magnesium was evaluated by validated food questionnaires assessing the risk of T2DM (Schulze et al., 2007). In light of the evidence from this investigation and a meta-analysis including various previous studies, the authors summarised that higher magnesium intake, along with higher fiber consumption, might be able to decrease the risk of developing T2DM. A recent meta-analysis of epidemiological studies with more than 500,000 participants affirmed a diabetes risk reduction by 14% with every 100 mg increase in daily magnesium intake (Dong et al., 2011).

The ARIC study (Peacock et al., 2010) also reported a significant reduction of sudden cardiac death in the group of participants with high plasma magnesium concentration. Compared to the lowest quartile the participants in the upper quartile of plasma magnesium concentrations had a 55% lower risk. This result is supported by a case control study in a subgroup of women from the Nurses' Health Study. Also in this study the risk for sudden cardiac death was reduced by 77% if the highest quartile of plasma magnesium concentration was compared to the lowest quartile (Chiuve et al., 2011).

These results were also confirmed by a study from Germany (Reffelmann et al., 2011). The Study of Health in Pomerania investigated a representative sample of the Northeast German population aged 20 to 79. Over a period of 10 years all occurring deaths in the cohort of 3910 persons were recorded. All cause mortality but especially also cardiovascular mortality was significantly increased by 40% in the group with plasma magnesium concentration below 0.73 mmol/L. This low magnesium concentration was found in 25% of the population.

The National Health and Nutrition Examination Survey Epidemiologic Follow-up Study also showed an inverse relationship of serum magnesium and mortality from coronary artery disease (CAD) (Ford et al., 1999). Another study, based on a cohort of 12708 participants of the ARIC study, showed that the average thickness of the carotid wall in women increased with each 0.1 mmol decline in serum magnesium levels (P = 0.006). A further result of the ARIC study was that low serum magnesium and high serum phosphorus and calcium were independently associated with greater risk of incident heart failure (Lutsey et al., 2014). Results from an observational study conducted in the general Japanese population (N = 728) demonstrated similar findings: lower serum magnesium levels were significantly and independently associated with a greater average intima-media thickness (P = 0.004) and the risk of at least two carotid plaques (P = 0.03) (Hashimoto et al., 2010).

Generally an increased risk of cardiovascular disease was connected to a low magnesium intake or a low serum magnesium concentration as shown in a meta-analysis of 16 studies with data from more than 313.000 individuals (Del Gobbo et al., 2013), a result that was also reported in a different meta-analysis from Qu et al. (2013).

Guasch-Ferré et al. (2014) reported an association between low magnesium intake and increased cardiovascular, cancer and mortality risk in a Mediterranean population. The study included 7216 men and women aged 55-80 y from the PREDIMED (Prevención con Dieta Mediterránea) study, a randomized clinical trial with a median follow-up of 4.8 y.

Furthermore, Ascherio et al., (1998) found a negative association between dietary magnesium intake and risk of stroke in a prospective study including 43738 individuals. In 2012 a meta-analysis from 7 studies with more than 241.000 participants reported that dietary magnesium intake was inversely associated with the risk of stroke (Larsson et al., 2012).

Module SI.2 Concomitant medication(s) in the target population

Bagis et al tested the effect of oral magnesium citrate or amitriptyline alone and in combination on symptoms of fibromyalgia. Patients were divided into 3 groups, receiving magnesium citrate (magnesium 300mg/day; N = 20) or amitriptyline (10mg/day; N = 20) alone or in combination (magnesium 300mg/day + amitriptyline 10mg/day; N = 20). Pain intensity, pain threshold, the number of tender points, the tender point index, the fibromyalgia impact questionnaire (FIQ), the Beck depression and Beck anxiety scores as well as serum and erythrocyte magnesium levels were evaluated at baseline and after 8 weeks of treatment. The number of tender points, tender point index, FIQ and Beck depression scores decreased significantly with the magnesium citrate treatment, serum and erythrocyte magnesium levels increased significantly with the magnesium citrate treatment (Bagis et al., 2012).

Kuipers et al reported case of a 76-years old female patient with muscle cramps and lethargy caused by hypomagnesaemia and hypocalcaemia with a low parathyroid hormone level while using of esomeprazole a proton pump inhibitor (PPI).

Electrolyte status was restored by infusion, the patient was treated with 3x500 mg oral magnesium oxide for 2 months. No adverse drug reactions were reported. Two months later the. Within four weeks after magnesium was discontinued a dramatic drop in the serum magnesium and calcium followed. This suggests a total body magnesium deficiency due to continued intake of esomeprazole. This case report shows, that the tratment of a PPI leads to an increased renal magnesium loss with severe hypomagnesiaemia, which can be prevented by a concomitant supplementation of oral magnesium (Kuipers et al. 2009).

A study of Gallelli et al. evaluated both the effects of ibuprofen and/or acetaminophen for the acute treatment of primary migraine in children in or out prophylactic treatment with magnesium. Magnesium oxide increased the efficacy of ibuprofen and acetaminophen with not age-related effects (Gallelli et al. 2013).

A study was performed in 89 children with stable bronchial asthma to investigate the magnesium status and the effect of 12 weeks of magnesium citrate therapy (200-290 mg/d) on the use of bronchodilators. Children with moderate asthma benefited greatly from long-term prophylaxis with magnesium and the use of bronchodilators decreased significantly in the magnesium group compared to the placebo group after 8 and 12 weeks respectively (Bede et al. 2003).

The effects of magnesium supplementation were tested in 20 patients with essential hypertension receiving long-term thiazide diuretic treatment and 21 age-matched untreated patients. The magnesium supplemented group received magnesium oxide (600 mg Mg/day) for 4 weeks. During magnesium supplementation, there were significant decreases in intra-erythrocyte sodium content and mean blood pressure and increases in red cell magnesium content and the sodium efflux rate constant. These results indicate that long-term diuretic treatment may give rise to intracellular magnesium deficiency and a suppression of cell membrane active sodium transport. The results also suggest that oral magnesium may decrease intracellular sodium, which in turn may contribute to the reduction in. blood pressure. Therefore, magnesium supplementation may be a worthwhile additional therapy for diuretics (Hattori et al. 1988).

Module SI.3 Important co-morbidities found in the target population

Overall, since hypomagnesaemia is a quite unspecific pathological phenomenon potentially triggered by a variety of underlying conditions, no specific pattern of co-morbidities could be identified. However, there are several disease patterns associated with a manifestation of magnesium deficiency (hypokalaemia, hypocalcaemia, neuromuscular hyperexcitability, electrocardiographic abnormalities, cardiac arrhythmias).

PART II MODULE SII-SIV:

According to Guideline on good pharmacovigilance practices (GVP) V.C.3.1. for new applications under Article 10a of Directive 2001/83/EC, RMP modules SII - SIV may be omitted.

PART II: MODULE SV-POST-AUTHORISATION EXPERIENCE

Magnesium Diasporal 400 mg direkt is not authorised yet. However, magnesium preparations have been applied for many decades worldwide to cover increased magnesium requirements and for the prevention and treatment of magnesium deficiency. Magnesium oxide as well as magnesium citrate is in well-established use since many years as medicinal product in several European countries.

The pharmacological and clinical trials and post-marketing experience data available from scientific literature provide proof for treatment and prevention of magnesium deficiency with regard to both efficacy and safety. According to these data, a dose of 400 mg magnesium administered once daily is reasonable for magnesium supplementation. Therefore, Magnesium Diasporal 400 mg direkt could be used as a therapeutic alternative to currently available drugs because it is designed to improve or prevent from magnesium deficiency. The pharmaceutical form “granules”, the intake once a day without water and the pleasant taste may lead to a good compliance and therefore therapeutic success.

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

Not applicable.

SV.2 Non-study post-authorisation exposure

Not applicable.

SV.3 Post-authorisation use in populations not studied in clinical trials

Not applicable.

SV.4 Post-authorisation off-label use

Not applicable.

SV.5 Epidemiological study exposure

During recent years, several large epidemiological studies have been published suggesting a risk reducing effect of a high magnesium intake and/or a low plasma magnesium concentration with regard to various diseases or an increased risk with low intake.

More details to epidemiologic studies can be found in Module SI: *Epidemiology of the indication(s) and target population(s).*

Study title and study type (e.g. cohort or case/control)	**Objectives**	**Population studied (data source and country)**	**Duration (study period)**	**Number of persons (in each group or of cases and controls) and person time (if appropriate)**	**Comment**
Kao et al. 1999: Serum and Dietary Magnesium and the Risk for Type 2 Diabetes Mellitus cohort study	Assessment if risk for type 2 diabetes is associated with low serum magnesium level and low dietary magnesium intake	USA	6 years follow-up	12128 nondiabetic middleaged adults	
Lopez-Ridaura *et al.* 2004: Magnesium Intake and Risk of Type 2 Diabetes in Men and Women cohort study	To examine the association between magnesium intake and risk of type 2 diabetes.	USA	18 years follow up (female persons), 12 years follow-up for male participations	85,060 women, 42,872 men with no history of diabetes, cardiovascular disease, or cancer at baseline	
Song *et al.* 2006): Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials Meta-analysis	The aim of this study was to assess the evidence on the effect of oral magnesium supplementation on glycaemic control in patients with Type 2 diabetes.	USA	4-16 weeks	370 patients with Type 2 diabetes	
Ford 1999: Serum magnesium and ischaemic heart disease: findings from a national sample of US adults Cohort-study	Association between serum magnesium concentration and mortality from ischaemic heart disease (IHD) or all-causes	USA	19 years follow-up	12 340 IHD and 12 952 all-cause-mortality participants	

Peacock *et al.* 2010: Serum Magnesium and Risk of Sudden Cardiac Death in the Atherosclerosis Risk in Communities (ARIC) Study Cohort-study	Association of serum magnesium (Mg) with increased risk of sudden cardiac death (SCD).	USA	12 years follow-up	14,232 45–64 year old African-Americans	
Reffelmann *et al.* 2011: Low serum magnesium concentrations predict cardiovascular and all-cause Mortality Cohort-study	All-cause mortality and cardiovascular mortality were analyzed in relationship to serum magnesium concentrations	West Pomerania (Germany)	5-year-follow-up	3910 health subjects	
Lutsey et al., 2014: Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. Cohort-study	Test of hypotheses that the incidence of HF is greater among individuals with low serum magnesium and those with high serum phosphorus and calcium.	USA	20-22 years	14,709 participants from ARIC study	
Del Gobbo et al., 2013: Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies Meta-Analysis	Investigation of prospective associations of circulating and dietary magnesium with incidence of cardiovascular disease (CVD), including fatal ischemic heart disease (IHD) and fatal IHD.	USA Finland Germany Sweden Japan France Wales	NA	313,041 individuals and 11,995 CVD, 7534 IHD, and 2686 fatal IHD events.	
Qu et al. 2013: Magnesium and the Risk of Cardiovascular Events: A Meta-Analysis of Prospective Cohort Studies	Evaluation of the association between dietary magnesium intake and serum magnesium concentrations and the risk of total CVD events.	USA Germany China France Sweden Finland	NA	532,979 participants from 19 studies	

Guasch-Ferré et al. (2014):Dietary Magnesium Intake Is Inversely Associated with Mortality in Adults at High Cardiovascular Risk Cohort-Study	The aim of this study was to assess the association between magnesium intake and CVD and mortality risk in a Mediterranean population at high cardiovascular risk with high average magnesium intake.	Spain	4.8 years of follow-up	7216 male and female individuals with one of two Mediterranean diets (supplemented with nuts or olive oil) or advice on a low-fat control diet	

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for harm from overdose

In the case of intact renal function, magnesium intoxication due to oral overdose of magnesium cannot be expected. Only in the case of severe renal insufficiency, accumulation of magnesium may arise. Further information upon risks associated with accumulation of magnesium is presented in Part II: *Module SVII Identified and* potential risks.

Therapeutic intervention in case of an acute magnesium overdose is described as follows: Intravenous administration of calcium and slow intravenous administration of 0.5 – 2 mg neostigminmetilsulfat; intravenous and per-osseous administration of isotonic sodium chloride solution; ventilatory circulatory support; in case of renal insufficiency: haemodialysis.

SVI.2 Potential for transmission of infectious agents

During the manufacturing process of Magnesium Diasporal 400 mg direkt no pharmaceutical ingredients with infectious potential, such as plasma components, are involved. In conclusion, Magnesium Diasporal 400 mg direkt carries no potential for transmission of infectious agents.

SVI.3 Potential for misuse for illegal purposes

Magnesium Diasporal 400 mg direkt has no addictive potential such as dependence and tolerance, thus the potential for misuse for illegal purposes is negligible.

SVI.4 Potential for medication errors

No relevant medication errors were identified during the clinical trials that were published in the literature. Therefore the likelihood of medication errors seems to be low.

SVI.5 Potential for off-label use

Magnesium Diasporal 400 mg direkt is indicated for the treatment and prevention of magnesium deficiency.

It cannot be excluded that Magnesium Diasporal 400 mg direkt may be used also for the treatment or prevention of other dietary or nutritional disorders in combination with any dietary supplements or other drugs. Given that the individual safety and efficacy profile of magnesium oxide and magnesium citrate is well characterised in a variety of published clinical studies as well as non-clinical studies, no additional discernible risks are identified if Magnesium Diasporal 400 mg direkt is to be used off-label.

SVI.6 Specific paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

Not applicable

SVI.6.2 Potential for paediatric off-label use

The safety and efficacy of Magnesium Diasporal 400 mg direkt in children has not been established. There are studies concerning the use of magnesium oxide or magnesium citrate in children available (Wang et al., 2003; Unachak et al., 2003; Bircan et al., 2006; Carpenter et al., 2006), but these data are not sufficient to justify the specific paediatric use. Therefore, Magnesium Diasporal 400 mg direkt will be for use in adults > 18 years only. However, given the outlined safety data, no additional discernible risks are considered if Magnesium Diasporal 400 mg direkt is to be used off-label in the paediatric population.

SVI.7 Conclusions

Safety concerns from this module	
Safety concern	Comment
Side effects associated with increased plasma concentration of magnesium	Only in patients with serious renal insufficiencies, elevated serum magnesium levels can occur that might lead to toxic symptoms.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

Adverse events/adverse reactions

During the last 25 years, overall 43 clinical studies on the oral use of magnesium oxide and/or magnesium citrate in humans with relevance for the current benefit/risk assessment were found in literature databases and integrated into this assessment. Of a total of 2183 volunteers, 862 with magnesium oxide and 756 were treated with magnesium citrate. Adverse drug reactions were documented in altogether 127 cases, 56 with magnesium oxide and 71 with magnesium citrate. The concentration range of the oral magnesium doses was between 4 mmol and 36 mmol magnesium/day equivalent to 100 mg and 900 mg magnesium (Carpenter et al., 2006; Esfanjani et al., 2012; Wang et al., 2003; van Laecke et al., 2014; de Lourdes Lima et al., 1998; Ridgway et al., 1990; Borrello et al., 1996; Lee et al., 2009; Fuentes et al., 2006; Lal et al 2003; Veronese et al. 2014; Roffe et al. 2002; Shechter et al. 2003; Dumont et al. 2004; Pokan et al. 2006; Köseoglu et al. 2008; Aydin et al., 2010; Shechter et al., 2012; Wilimzig and Pannewig 1994).

All adverse drug reactions of magnesium oxide and/or magnesium citrate were non-serious, and most of them were basically related to diarrhoea or soft stool. Adverse drug reactions were comparable in all studies.

Postmarketing information of Magnesium-Diasporal 150, Magnesium-Diasporal 100, Magnesium Diasporal 400 EXTRA direkt: patient exposure and adverse drug reaction reports

Comparable magnesium preparations with the identical active ingredients magnesium oxide or magnesium citrate have been applied for many years in European countries, e.g. as Magnesium-Diasporal 150, capsules or Magnesium-Diasporal 100, lozenges.

The use and tolerance for multiple dose of 300 mg magnesium from magnesium oxide can be demonstrated on the basis of the reference products Magnesium Diasporal 150, capsules (Protina Pharmazeutische GmbH, Ismaning, Germany).

The daily dose for the Magnesium Diasporal 150, capsules in Germany is 2 capsules per day equal to 300 mg magnesium from magnesium oxide. The number of sold daily doses of Magnesium Diasporal 150 in Germany over the last 12 years (12/2002 – 12/2014) was 66,846,500 daily doses, which is in accordance with 183,142 patient years. Over this time period of 12 years, 11 ADR in association with Magnesium Diasporal 150 were reported to the company. All of them were non-serious. A direct causal relationship can be established for 5 ADR concerning gastrointestinal disorders. There was no causality given for the 6 ADR concerning allergy (N = 5) or dry mouth (N = 1).

The use and tolerance for the single dosage of 400 mg magnesium from magnesium citrate can be demonstrated on the basis of the reference products Magnesium Diasporal 100, lozenges (Protina Pharmazeutische GmbH, Ismaning, Germany).

The daily dose for the Magnesium Diasporal 100, lozenges in Austria is 3 – 4 lozenges per day equal to 300 – 400 mg magnesium. The number of sold daily doses of Magnesium Diasporal 100 in Austria over the last 12 years (12/2002 – 12/2014) was 37,202,850 daily doses, which is in accordance with 101,925 patient years. Over this time period of 12 years, no ADR in association with Magnesium Diasporal 100 was reported to the company.

The use and tolerance for the single dosage of 400 mg magnesium from magnesium oxide and magnesium citrate can be demonstrated on the basis of the reference product Magnesium Diasporal 400 EXTRA direkt (Protina Pharmazeutische GmbH, Ismaning, Germany).

Magnesium Diasporal 400 EXTRA direkt is sold as food supplement in Germany since July, 2011 and in Austria since January, 2012. The daily dose for the Magnesium Diasporal 400 EXTRA direkt is one stick per day equal to 400 mg magnesium from magnesium oxide and magnesium citrate. The number of sold daily doses of Magnesium Diasporal 400 EXTRA direkt in Germany over the last 3.5 years (07/2011 – 12/2014) was 48,151,620 daily doses which is in accordance with 131,922 patient years. The number of sold daily doses of Magnesium Diasporal 400 EXTRA direkt in Austria over the last 3 years (01/2012 – 12/2014) was 1,084,538 daily doses which is in accordance with 2971 patient years. Although Magnesium Diasporal 400 EXTRA is a food supplement, the company records undesirable accessory symptoms (UAS). Over this time period of 3.5 years, 8 UAS in association with Magnesium Diasporal 400 EXTRA direkt from Germany were reported to the company. All of them were non-serious concerning diarrhea (N = 5), allergy (N = 2) or tooth discolouration (N = 1). No UAS in association with Magnesium Diasporal 400 EXTRA direkt from Austria was reported to the company.

SVII.1 Newly identified safety concerns (since this module was last submitted)

Not applicable. This is the first RMP.

SVII.2 Recent study reports with implications for safety concerns.

Not applicable.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience

Identified risks

Identified risk	Gastrointestinal adverse reactions
Seriousness/outcomes	All GI adverse events reported in literature were non-serious. GI adverse reactions are generally considered reversible. However, no sufficient information on outcomes of the reported events was provided in the available published studies.
Severity and nature of risk	According to the available data GI effects associated with the use of oral magnesium are generally considered to be of low severity.
Frequency	With reference to the total number of subjects enrolled in clinical studies on magnesium oxide during the period covered by this report (N = 862), the frequency of adverse drug reaction associated with magnesium oxide is 5.92 % for diarrhea and soft stool, 0.35 % for not qualified abdominal pain. Itching appeared in 0.23 % of cases, however a causal relationship with the oral use of magnesium oxide is unlikely. With reference to the total number of subjects enrolled in clinical studies on magnesium citrate during the period covered by this report (N = 756), the frequency of adverse drug reactions known to be associated with magnesium citrate was 8.47 % for diarrhea and soft stool, 0.53 % for not qualified gastric irritations and nausea as well as 0.40 % for not qualified abdominal pain. No further serious or non-serious, listed or unlisted adverse drug reactions from published studies were reported.
Background incidences/prevalence	Gastrointestinal disorder incidence/prevalence in magnesium-deficient population is assumed to be mainly dose-dependent with respect to patient's individual sensitivity to the active substance.
Risk groups or risk factors	As the kidneys play a crucial role in magnesium homoeostasis, in advanced chronic kidney disease, the compensatory mechanisms start to become inadequate and hypermagnesaemia may develop. Symptomatic hypermagnesaemia may be caused by excessive oral administration of magnesium salts when renal function declines (Hashizume and Mori 1990; Mordes and Wacker 1977; Swaminathan 2003). Therefore, only in patients with serious renal insufficiencies, elevated serum magnesium levels can occur that might lead to toxic symptoms. Use of magnesium should be avoided when renal function is severely limited (GFR < 30 mL/min).
Potential mechanisms	When higher doses are administered, osmotical diarrhoea may occasionally occur. However, diarrhoea induced by easily dissociable magnesium salts is completely reversible within 1 to 2 days and does not represent a significant health risk in subjects with intact renal function (EFSA 2006). Generally only part (30 – 70 %) of the ingested magnesium is absorbed. The remaining magnesium and the counter ion binds water in the intestines leading to stool softening and reduced gastric transit times in sensitive persons.
Preventability	By mechanism of action, occurrence of GI side effects can be avoided if administered as indicated in the current draft SPC of Magnesium Diasporal 400 mg direkt. According to the Magnesium Diasporal 400 mg direkt draft SPC the therapy should be temporarily interrupted and can be assimilated after improvement and/or elimination of the symptoms with a reduced dosage. The

	use of Magnesium Diasporal 400 mg direkt is contraindicated in patients with serious kidney dysfunctions as mentioned in the SPC.
Potential public health impact of safety concern	In general, magnesium, administered orally, is well tolerated. Diarrhoea induced by easily dissociable magnesium salts is completely reversible within 1 to 2 days and does not represent a significant health risk in subjects with intact renal function (EFSA 2006).
Evidence source	Epidemiological and clinical studies from literature.
Medra Term	Gastrointestinal disorders (Medra Code 10017947)

Potential risks

Potential risk	**Side effects associated with increased plasma concentration of magnesium**
Seriousness/outcomes	No adverse events associated with a markedly increased plasma concentration of magnesium were reported in any of the published studies.
Severity and nature of risks	As the kidneys play a crucial role in magnesium homoeostasis, in advanced chronic kidney disease, the compensatory mechanisms start to become inadequate and hypermagnesaemia may develop. Symptomatic hypermagnesaemia may be caused by excessive oral administration of magnesium salts when renal function declines (Hashizume and Mori 1990; Mordes and Wacker 1977; Swaminathan 2003). Therefore, only in patients with serious renal insufficiencies, elevated serum magnesium levels can occur that might lead to toxic symptoms. Use of magnesium should be avoided when renal function is severely limited (GFR < 30 mL/min). When there is a marked increase in the plasma concentration of magnesium in some cases following oral intake of extremely high doses or in patients with severe renal insufficiency or ileus, the following adverse effects may be seen: blood pressure fall, nausea, vomiting, hyporeflexia, and somnolence, changes in the electrocardiogram, respiratory depression and cardiac arrest. In the case of intact renal function, magnesium intoxication due to oral overdose of magnesium cannot be expected. Only in the case of severe renal insufficiency, accumulation of magnesium may arise.
Frequency	Not applicable.
Background incidences/prevalence	Only in patients with serious renal insufficiencies, elevated serum magnesium levels can occur that might lead to toxic symptoms.
Risk groups or risk factors	Patients of risk for renal insufficiency of any aetiology should be considered as risk groups.
Potential mechanisms	When there is a marked increase in the plasma concentration of magnesium in some cases following oral intake of extremely high doses or in patients with severe renal insufficiency, the following adverse effects may be seen: blood pressure fall, nausea, vomiting, hyporeflexia, somnolence, changes in the electrocardiogram, respiratory depression and cardiac arrest. Please also refer

	to current draft SPC of Magnesium Diasporal 400 mg direkt.
Preventability	High magnesium plasma concentrations are generally only considered in terms of overdose of magnesium associated with renal dysfunction. The use of Magnesium Diasporal 400 mg direkt is contraindicated in patients with serious kidney dysfunctions and in patients with disorders of conduction on the heart that causes slow heartbeat (bradycardia). Considerable high plasma concentrations by ingestion of large amounts of magnesium should generally be avoided.
Potential public health impact of safety concern	In general, when administered in doses as indicated, no increased risk of toxicity associated with high plasma concentrations of magnesium is considered. The results from safety data available to date do not indicate an increased risk under the use of oral magnesium oxide or magnesium citrate as active substances.
Evidence source	Epidemiological and clinical studies from literature.

SVII.4 Identified and potential interactions including food-drug and drug-drug interactions

SVII.4.1 Overview of potential for interactions

Several pharmaceutical drugs influence the excretion or absorption of magnesium (Lameris *et al.* 2012). In case of drug-induced hypomagnesaemia caused by concomitant treatment with one of the following drugs, dose adjustment of Magnesium Diasporal 400 mg direkt should be considered.

SVII.4.2 Important identified and potential interactions

Interacting substance(s)	**osmotic diuretics, loop diuretics and thiazide-type diuretics**
Effect of interaction	Hypomagnesaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	Osmotic diuretics diminish salt and water reabsorption by increasing the flow rate thereby reducing serum magnesium levels. Loop diuretics (such as furosemide, bumetanide, torsemide and ethacrynic acid) lead to renal magnesium wasting and hypomagnesaemia due to reduced paracellular magnesium reabsorption (Quamme and de Rouffignac 2000). Thiazide treatment leads to hypomagnesaemia as well as hypocalciuria (Efstratopoulos et al. 1997; Grieff and Bushinsky 2011). However, the effect of thiazides on magnesium reabsorption only becomes apparent upon chronic treatment (Nijenhuis et al. 2005).
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**epidermal growth factor (EGF) antagonists (e.g. cetuximab and erlotinib**

Effect of interaction	Hypomagnesaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	EGF stimulates the trafficking of TRPM6 channels to the luminal membrane, increasing the reabsorption of magnesium through TRPM6(Thebault et al. 2009).
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Proton pump inhibitors (e.g. omeprazole and pantoprazole)**
Effect of interaction	Hypomagnesaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	disturbances in magnesium absorption (probably) (Epstein et al. 2006, Cundy and Dissanayake, 2008; Kuipers et al., 2009; Hoorn et al., 2010; Furlanetto and Faulhaber, 2011)
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Aminoglycoside antibiotics (e.g. gentamycin, tobramycin and amikacin)**
Effect of interaction	Hypomagnesaemia
Evidence source	Epidemiological and clinical studies from literature.

Possible mechanisms	renal magnesium loss (Giapros et al. 1995; Shah and Kirschenbaum 1991)
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**pentamidine**
Effect of interaction	Severe hypomagnesaemia and hypocalcemia (Gradon et al. 1991; Mani 1992)
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	renal magnesium wasting
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Rapamycin**
Effect of interaction	Hypomagnesaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	increased renal magnesium excretion (Andoh et al. 1996)
Potential health risk	Clinical symptoms of magnesium deficiency

Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Amphotericin B**
Effect of interaction	Hypomagnesaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	Amphotericin B causes renal injury leading renal insufficiency, urinary K+ wasting and hypokalaemia, magnesium wasting and hypomagnesaemia, metabolic acidaemia due to distal renal tubular acidosis, and polyuria (Laniado-Laborin and Cabrales-Vargas 2009)
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Foscarnet**
Effect of interaction	Hypomagnesaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	physical interaction between foscarnet and magnesium (chelate complexing) (Huycke et al. 2000; Stünzi and Perrin 1979)
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Calcineurin inhibitors (cyclosporin/A, FK506)**
Effect of interaction	Hypomagneaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	Tubular dysfunction (Barton et al. 1987; Scoble et al. 1990).
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Cisplatin**
Effect of interaction	Hypomagneaemia
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	Renal magnesium wasting due to nephrotoxicity (Lajer and Daugaard 1999, Ariceta et al. 1997; Bearcroft et al. 1999).
Potential health risk	Clinical symptoms of magnesium deficiency
Discussion	Comedication with magnesium is indicated. The dosage should be adjusted individually.

Interacting substance(s)	**Fluorides**
Effect of interaction	Reduced absorption of fluoride and/or magnesium

Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	Mutual influence of absorption (Cerklewski 1987;).
Potential health risk	Clinical symptoms of magnesium deficiency and reduced effect of fluorides.
Discussion	A 2 to 3 hour interval should therefore be observed between administrations of magnesium and fluorides.

Interacting substance(s)	**Tetracyclines**
Effect of interaction	Reduced absorption of tetracyclines and/or magnesium
Evidence source	Epidemiological and clinical studies from literature.
Possible mechanisms	Mutual influence of absorption (Ogawa and Echizen 2011)
Potential health risk	Clinical symptoms of magnesium deficiency and/or reduced antibiotic effect of tetracyclines
Discussion	A 2 to 3 hour interval should therefore be observed between administrations of magnesium and tetracyclines.

SVII.5 Pharmacological class effects

The pharmacological and clinical profile of magnesium oxide and magnesium citrate is well established and is considered as having a well-established use. The identified and potential risks are already described in this section. There are no additional relevant risks or safety concerns which can be derived from pharmacological class effects.

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

Not applicable

SVII.5.2 Important pharmacological class effects not discussed above

Not applicable

PART II: MODULE SVIII- SUMMARY OF THE SAFETY CONCERNS

There are no ongoing safety concerns.

Summary of safety concerns

Summary of safety concerns	
Important identified risks	Gastrointestinal adverse reactions
Important potential risks	Side effects associated with increased plasma concentration of magnesium due to severe renal impairment
Missing information	None

PART III PHARMACOVIGILANCE PLAN

Magnesium Diasporal 400 mg direkt has a well characterised safety profile with no special or unknown risk beyond those that has been documented in the submitted clinical data derived from published literature in respect of magnesium oxide and magnesium citrate.

ROUTINE PHARMACOVIGILANCE PRACTICES

Routine pharmacovigilance activities are performed according to the requirements set out in the guidelines on Good Pharmacovigilance Practice (GVP). A summary of the implemented pharmacovigilance system has been provided as part of the dossier submitted as application for marketing authorisation. The complete Pharmacovigilance System Master File is available on request.

Applied written procedures include, but are not limited to:

- Collection, collation, evaluation and regulatory reporting of spontaneous individual case safety reports (ICSR) – expedited and periodic reporting to authorities worldwide
- Collection and processing of ICSRs from post-marketing studies
- Follow-up and case-management practice ensuring high quality reports
- Production of periodic safety update reports (PSURs) *
- Ongoing monitoring and signal detection activities
- Risk management via corporate safety monitoring committee
- Training of company personnel
- Handling reports of defects in manufacture as they relate to patient safety

All pharmacovigilance activities are reviewed at regular intervals to ensure compliance with relevant legislation or changes within the company organisation.

Important identified risks: Gastrointestinal adverse reactions		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
non	routine pharmacovigilance	

* Production of PSURs is described in the PSMF, however PSUR submission is not necessary as magnesium oxide and magnesium citrate are in well-established use.

Important potential risks: Side effects associated with increased plasma concentration of magnesium due to severe renal impairment		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
non	routine pharmacovigilance	

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES TO ASSESS EFFECTIVENESS OF RISK MINIMISATION MEASURES

Additional pharmacovigilance activities are not planned.

III.3 STUDIES AND OTHER ACTIVITIES COMPLETED SINCE LAST UPDATE OF PHARMACOVIGILANCE PLAN

Not applicable.

III.4 DETAILS OF OUTSTANDING ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no outstanding additional pharmacovigilance activities

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Additional pharmacovigilance activities are not planned.

* Production of PSURs is described in the PSMF, however PSUR submission is not necessary as magnesium oxide and magnesium citrate are in well-established use.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIESNo post-authorisation efficacy trials are planned.

IV.1 Applicability of efficacy to all patients in the target population

Not applicable.

IV.2 Tables of post-authorisation efficacy studies

Not applicable.

IV.3 Summary of Post authorisation efficacy development plan Not applicable.

IV.4 SUMMARY OF COMPLETED POST AUTHORISATION EFFICACY STUDIES

Magnesium supplementation is used to treat patients with magnesium deficiency. The diagnosis of magnesium deficiency relies on three columns: clinical symptoms, risk of magnesium deficiency (induced by low dietary intake, comorbidities or drug-induced) and determination of plasma-magnesium concentration (Spätling *et al.* 2000).

The broad range of effects occurring in magnesium deficiency can lead to different clinical symptoms. In addition, some groups of subjects are at special risk to suffer from magnesium deficiency. In the following, the effects of magnesium oxide and magnesium citrate supplementation in various clinical settings are reported.

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (Completed, Study report submitted)	Date of submission of final study report
Prospective, placebo-controlled, randomized, one-year double-blind trial	Effect of magnesium oxide supplementation on bone mineral content (BMC) in healthy girls.	3% greater increase in the overall hip measures of BMC during the year of therapy with magnesium compared with placebo	Completed and published Carpenter et al., 2006	December 2006
Clinical study	Effects of daily oral magnesium citrate supplementation on biochemical markers of bone turnover	Oral magnesium supplementation caused significantly decrease in serum iPTH levels in the Mg-supplemented group ($p<0.05$). Serum osteocalcin levels were significantly increased ($p<0.001$) and urinary deoxypyridinoline levels were decreased ($p<0.001$) in the Mg-supplemented group.	Completed and published Aydin et al., 2010	June 2009

Clinical study	Effects of magnesium, L-carnitine, and concurrent magnesium–L-carnitine supplementation in migraine prophylaxis	The mean number of migraine frequency, severity, and index significantly decreased in all studied groups in comparison with that of the preintervention, with the highest reduction in the magnesium supplemented group ($p<0.001$). The mean migraine days/ month in migrainous patients decreased significantly in all study groups ($p<0.001$). Oral supplementation with magnesium oxide and L-carnitine and concurrent supplementation of Mg–L-carnitine besides routine treatments could be effective in migraine prophylaxis.	Completed and published. Tarighat Esfanjani et al., 2012	August 2012
Randomized, double-blind, placebo-controlled trial	Assessment if oral magnesium oxide reduces migrainous headache frequency, severity and associated features in children.	Statistically significant decrease over time in headache frequency in the magnesium oxide group (P =.0037) but not in the placebo group (P =.086). The group treated with magnesium oxide had significantly lower headache severity (P=.0029) relative to the placebo group.	Completed and published. Wang et al., 2003	January 2003
Double-blind, placebo-controlled study	Effect of magnesium citrate for migraine prophylaxis	Frequency of migraine attacks was significantly reduced in the magnesium group [1.51 (41.6%)] compared to the placebo group [0.58 (15.8%)] The reduction of the number of migrain days was also significantly reduced in the magnesium group [2.49(52.3%)] compared to placebo.	Completed and published. Peikert et al., 1996	February 1996
Randomized, double-blind, placebo-controlled trial	Effects of magnesium prophylaxis in migraine without aura	In a comparison of the effects of magnesium citrate treatment with those of placebo, post/pretreatment ratios of migraine attack frequency, severity and P1 amplitude in Mg treatment group were found to be significantly lower than those in placebo treatment group (attack frequency $p = 0.005$, attack severity $p < 0.001$, P1 amplitude $p < 0.05$).	Completed and published. Köseoglu et al.	2008
Open clinical trial.	Effect of magnesium oxide on periodic limb movements during sleep (PLMS) with and without symptoms of restless leg syndrome (RLS)	Following magnesium oxid treatment, PLMS associated with arousals (PLMS-A) decreased significantly (17 +/- 7 vs 7 +/- 7 events per hour of total sleep time, $p < 0.05$). PLMS without arousal were also moderately reduced (PLMS per hour of total sleep time 33 +/- 16 vs 21 +/- 23, $p = 0.07$). Sleep efficiency improved from 75 +/- 12% to 85 +/- 8% ($p < 0.01$). In the group of patients estimating their sleep and/or symptoms of RLS	Completed and published. Hornyak et al.	May 1998

		as improved after therapy (n = 7).		
Case report	Effect of magnesium oxide supplementation on hypomagnesaemia and neurological disorders	A 39-old woman with short-bowel syndrome and stoma presented paraesthesia as well as cramps in hands and feet, dehydration with positive Trousseau's and Chovstek's signs, neurological examination was otherwise normal. Among others, she was given intravenous magnesium , followed by oral magnesium glycerophosphate which failed to maintain serum magnesium levels. Serum magnesium stabilized only after treatment with magnesium oxide 3 x 100 mg 9-times/day.	Completed and published. Ross et al.	2011
Case report	Primary hypomagnesemia in a 10 week old, female infant suffering from recurrent convulsions	Oral magnesium sulfate given irregularly caused frequent loose stool and black staining of the teeth. Switch from magnesium sulfate to magnesium oxide resulted in an increase level of serum magnesium and the gradual disappearance of the black staining of the teeth and frequent loose stool. Oral magnesium dosage of 15 mg/kg/day led to adequate serum levels and kept patient free from convulsions.	Completed and published. Unachak et al.	January 2002
Randomized double-blind study	Efficacy of magnesium citrate versus placebo in the treatment of nocturnal leg cramping	A trend towards fewer cramps was observed in the magnesium group, but was not significant (p = 0.07). In the magnesium group, nocturnal leg cramping tended to occur more rarely than in the placebo group and significantly more patients in the magnesium group noticed an improvement in their symptoms	Completed and published. Roffe et al.	May 2002
Single-center, open-label, randomized parallel group study,	Effectiveness of oral magnesium for improving glycemic control and insulin sensitivity at 3 months post-transplantation (kidney).	In patients randomized to magnesium oxide versus no treatment, fasting glycemia on average was 11.5 mg/dl lower (95% CI 1.7 to 21.3; P = 0.02)	Completed and published. Van Laecke et al	February 2014
Clinical study	Effect of magnesium oxide supplementation on the lipid profile and blood glucose of patients with Type 2 Diabetes (T2DM)	Magnesium supplementation led to a significant decrease in total cholesterol, Low-density lipoprotein (LDL) cholesterol and triglycerides as well as an increase in High-density lipoprotein (HDL) cholesterol levels. Fasting and post-prandial glucose levels did not change to baseline.	Completed and published. Lal et al.	April 2003
Randomized double-blind study	Effect of glucose/insulin infusion and magnesium supplementation on	Oral magnesium oxide supplementation significantly increased muscle potassium	Completed and published.	January 2003

	serum and muscle sodium and potassium and muscle [3H]ouabain binding capacity in type 1 diabetes patients	content (6%) in type 1 diabetes patients	Djurhuus et al	
Double-blinded, placebo-controlled trial	Effect of magnesium supplementation in increasing doses on the control of type 2 diabetes (T2DM)	Intracellular Mg in patients with diabetes was significantly lower than in the normal population (62 blood donors; 1.4 +/- 0.6 vs. 1.7 +/- 0.6 micrograms/mg of total proteins). In the placebo and in the 20.7 mmol Mg groups, no changes in plasma and intracellular levels and no improvement in glycemic control were observed. Replacement with 41.4 mmol Mg tended to increase plasma, cellular, and urine Mg and caused a significant fall (4.1 +/- 0.8 to 3.8 +/- 0.7 mmol/l) in fructosamine (normal, 1.87-2.87 mmol/l).	Completed and published. de Lourdes Lima et al.	January 1998
Randomized, double-blinded, placebo-controlled crossover trial	Effect of magnesium supplementation on molecular mechanisms of pleitropic metabolic action in overweight individuals	Magnesium treatment significantly decreased fasting C-peptide concentrations (change: 20.4 ng/mL after magnesium treatment compared with +0.05 ng/mL after placebo treatment; P = 0.004) and appeared to decrease fasting insulin concentrations (change: 22.2 lU/mL after magnesium treatment compared with 0.0 lU/mL after placebo treatment; P = 0.25).	Completed and published. Chacko et al.	December 2010
Double‐ blind, randomized clinical trial	Effect of magnesium oxide supplementation on primary insomnia in elderly.	As compared to the placebo group, in the experimental group, dietary magnesium supplementation brought about statistically significant increases in sleep time (P = 0.002), sleep efficiency (P = 0.03), concentration of serum renin (P < 0.001), and melatonin (P = 0.007), and also resulted in significant decrease of ISI score (P = 0.006), sleep onset latency (P = 0.02) and serum cortisol concentration (P = 0.008). Supplementation also resulted in marginally between‐ group significant reduction in early morning awakening (P = 0.08) and serum magnesium concentration (P = 0.06). Although total sleep time (P = 0.37) did not show any significant between‐ group differences.	Completed and published. Abbasi et al.	December 2012
Double-blinded, placebo-	Effect of magnesium supplementation on sleep quality and	Magnesium as well as placebo supplementation led to improvement of the Pittsburg Sleep	Completed and published.	2010

controlled trial	inflammatory markers	Quality Index and erythrocyte magnesium levels. In 37 participants with magnesium concentrations < 1.8 mg/dL, magnesium supplementation but not placebo significantly increased serum magnesium levels. Magnesium supplementation but not placebo decreased plasma C-reactive protein (CRP), a biomarker of inflammation.	Nielsen et al	
Case report	40 day-old female infant with severe hypomagnesaemia with secondary hypocalcaemia.	Patient was the patient was discharged with oral magnesium subcarbonate and intramuscular magnesium sulphate . On regular follow-up until the age of 4 y, the child was asymptomatic. During this 4-y period, oral Mg dose was gradually increased while the doses and frequency of administration of parenteral Mg were decreased. Additionally, oral Mg subcarbonate was switched to Mg citrate because of its side effects. Finally, parenteral Mg was discontinued, and the dosage of oral Mg supplementation reached a level of 90 mg/kg/d of elemental Mg citrate, without any gastrointestinal side effects. With 5 years the child was symptom free.	Completed and published. Bircan et al.	April 2006
placebo controlled, partially double-blinded, clinical trial	Comparison of a combination of evening primrose oil and fish oil with magnesium oxide and placebo in preventing preeclampsia.	The magnesium supplemented group had significantly the fewest number of cases of hypertension as well as the fewest cases of edema.	Completed and published. D'Almeida et al.	1992
prospective randomized trial	Comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis and side effects.	Numbers of preterm births were similar between the 2 groups. The authors conclude that oral magnesium oxide is as effective as terbutaline for the maintenance of tocolysis with fewer side effects and at lower costs.	Completed and published. Ridgeway et al.	September 1990
randomized, placebo-controlled trial	Effect of oral magnesium supplementation to prevent pregnancy-induced hypertension	Oral supplementation with 300 mg magnesium given as citrate decreased the risk of high diastolic blood pressure during the late phase of pregnancy.	Completed and published. Bullarbo et al.	May 2013
double-blinded, placebo-controlled, randomized trial	Effects of oral magnesium supplementation on insulin sensitivity and blood pressure (BP) in normomagnesemic, non-diabetic overweight	In subgroup analysis, magnesium supplementation lowered BP much more than placebo in those subjects whose systolic BP ≥ 140 mmHg, diastolic BP 80 - 90 mmHg, and diastolic BP ≥ 90mmHg at the start of the study.	Completed and published. Lee et al.	January 2009

	Korean adults.			
placebo-controlled, randomized trial	Effects of acute and chronic oral magnesium supplementation on endothelial function in patients with symptomatic heart failure.	Patients who received magnesium had improved small arterial compliance at 3 months from baseline compared with placebo. No significant differences in quality of life, exercise capacity or hemodynamic parameters could be observed.	Completed and published. Fuentes et al.	August 2005
placebo-controlled, randomized trial	Effects of magnesium oxide supplementation on mild hypertension and quality of life.	Magnesium oxide supplementation led to a significant reduction in systolic BP values at 12-week follow-up compared to pretreatment values and to placebo group. No difference was found in diastolic pressure or 24-hour noninvasive monitoring of BP. Magnesium supplementation also led to improved quality of life compared to placebo, with a corresponding significant improvement in psychosocial variables, general well-being, and work status.	Completed and published. Borrello et al.	October 1996
randomized crossover design	Effects of magnesium supplementation in hypertensive patients by measuring office, home and ambulatory BP.	BPs were significantly lower in the magnesium supplementation period than in the control period, although the differences were small. Serum concentration and urinary excretion of magnesium increased significantly with magnesium supplementation. Changes in 24-hour systolic and diastolic BPs were correlated negatively with baseline BP or changes in serum magnesium concentration.	Completed and published. Kawano et al.	March 1998
double-blind, randomized, cross-over study	Effects of oral magnesium supplementation on BP as well as sodium, potassium, calcium and magnesium intraerythrocyte concentrations.	Oral magnesium supplementation reduced significantly the systolic, diastolic and mean BP. Intraerythrocyte magnesium significantly increased whereas sodium concentration decreased.	Completed and published. Sanjuliani et al.	May 1996
Pre-/Post (placebo-controlled) study	Effects of oral magnesium oxide supplementation on high BP.	Magnesium supplementation led to a significant reduction in BP and a decrease in serum lipid concentrations (triglycerides, free fatty acids). In addition, magnesium supplementation induced a significant increase in serum magnesium concentration, intraerythrocyte magnesium and 24-h urinary magnesium excretion.	Completed and published. Motoyama et al.	March 1998
randomized prospective, double-blind,	Determination whether oral magnesium treatment inhibits	Median PDT was significantly reduced (35%) by oral magnesium oxide supplementation in contrast to	Completed and published.	2000

cross-over and placebo-controlled study	platelet-dependent thrombosis (PDT) in stable patients with coronary heart disease (CHD)	placebo. No effect on platelet aggregation was observed.	Shechter et al.	
randomized, placebo-controlled, double-blind study	Effect of oral magnesium replacement on duration of exercise tolerance in CHD patients.	Compared to placebo, the duration of exercise tolerance increased significantly in the magnesium group, exercise-induced chest pain decreased significantly and the patients' quality of life improved significantly.	Completed and published. Shechter et al.	March 2003
randomized, placebo-controlled, double-blind study	Effect of magnesium citrate in combination with 5.4 mmol potassium hydrocarbonate in patients with stable CAD	The oral magnesium citrate therapy over 6 months significantly increased intracellular magnesium levels and had a favourable effect on exercise tolerance and left ventricular function in stable CAD patients	Completed and published. Pokan et al.	August 2006
Randomized, controlled, trial	Evaluation of oral magnesium supplementation on serum magnesium and CRP, a biomarker of inflammation, in patients with chronic systolic heart failure (HF).	Oral magnesium supplementation to HF patient significantly attenuates blood levels of CRP	Completed and published. Almoznino-Sarafian et al.	May 2007
Randomized, controlled, trial	Effect of magnesium supplementation on HRV (heart rate variability) in normomagnesemic patients with systolic HF.	Magnesium administration in normomagnesaemic patients with systolic HF increases magnesium concentration and HRV correlation dimension (HRV CD). Magnesium supplementation may prove beneficial to HF patients.	Completed and published. Almoznino-Sarafian et al.	December 2008
randomized, double-blind, placebo-controlled, crossover study	Effect of magnesium oxide supplementation for 2 menstrual cycles in 38 women on the severity of premenstrual symptoms (PMS)	In the second month there was a significant reduction of symptoms of PMS-H (weight gain, swelling of extremities, breast tenderness, abdominal bloating) with magnesium supplementation compared with placebo.	Completed and published. Walker et al.	1998
Controlled trial	Effect of magnesium supplementation in pregnant for premature labour pain and in non-pregnant women for symptoms of dysmenorrhea was assessed.	Magnesium supplementation led to a significant decrease in very severe and severe dysmenorrhea symptoms.	Completed and published. Wilimzig und Pannewig et al.	1994
Pilot trial	Effects of magnesium oxide supplementation with high and low habitual dietary magnesium intake on resting and recovery from aerobic and resistance exercise and systolic blood pressure.	The supplemented group had a significant reduction in mean resting systolic blood pressure by 8.9 mmHg and post exercise by 13 mmHg. Recovery blood pressure was significantly lower (11.9 mmHg) in the intervention group compared to control and heart rate significantly decreased by 7 beats	Completed and published. Kass et al.	March 2013

		per minute in the magnesium group. Performance indicators did not change within and between the groups		
randomized, placebo-controlled trial	Test of the hypothesis that magnesium supplementation influences the physical performance of volleyball players.	Plasma magnesium decreased significantly only within the experimental group. Significant decreases in lactate production and significant increases in countermovement jump and countermovement jump with arm swing values were detected in the magnesium supplemented group, but not in the control group.	Completed and published. Setaro et al.	September 2013
randomized controlled, blinded trial	Investigation whether 12 week of oral magnesium oxide supplementation can improve physical performance in healthy elderly women.	After 12 week supplementation, the magnesium group had a significantly better total Short Physical Performance Battery score, chair stand times and 4-m walking speeds than the control group. Daily magnesium oxide supplementation for 12 weeks seems to improve physical performance in healthy elderly women. These findings suggest a role for magnesium supplementation in preventing or delaying the age-related decline in physical performance	Completed and published. Veronese et al.	June 2014
randomized, double-blinded study	Effects of magnesium on strength development during a double-blinded, 7-week strength training program.	Both groups gained strength, however, with a significant increase for the magnesium group compared to placebo in absolute pre and post quadriceps torque (QT), relative QT adjusted to body weight as well as lean body mass. Oral magnesium oxide supplementation resulted in a significant greater QT production of the quadriceps muscle group.	Completed and published. Brilla et al.	October 1991

Efficacy conclusions

As described in this section, magnesium oxide and magnesium citrate are used for treatment of many different symptoms of magnesium deficiency. Several diseases as well as special medical conditions such as migraine, diabetes, cramping, cardiovascular diseases, pregnancy and others are known to be related to magnesium deficiency. Altogether, the results of the clinical trials revealed that administration of magnesium oxide as well as magnesium citrate improves the medical condition of the subjects.

PART V: RISK MINIMISATION MEASURES

The pharmacological and clinical profile of magnesium oxide and magnesium citrate is well known and considered as having a well-established use.

As Magnesium Diasporal 400 mg direkt has a well-known safety profile, there is no proper basis to institute risk minimisation measures beyond the measures as described in this document and the proposed summary of product characteristics.

The safety profile for Magnesium Diasporal 400 mg direkt has been characterised on the basis of the submitted non-clinical and clinical data derived from published literature relating to the individual safety characteristics for magnesium oxide and magnesium citrate following decades of clinical use of this drug substances. All important and clinically relevant risks which are presented in this RMP are fully characterised in the draft SPC of Magnesium Diasporal 400 mg direkt.

V.1 RISK MINIMISATION MEASURES BY SAFETY CONCERN

Safety concern	Gastrointestinal adverse reaction
Objective(s) of the risk minimisation measures	
Routine risk minimisation measures	Proposed text in the PL in section 4: "If you get any side effects, you should temporarily interrupt the treatment. After the symptoms improve and/or are eliminated you can restart treatment with a reduced dosage."
Additional risk minimisation measure(s) (repeat as necessary)	NA

Safety concern	Important potential risks: Side effects associated with increased plasma concentration of magnesium due to severe renal impairment
Objective(s) of the risk minimisation measures	
Routine risk minimisation measures	Proposed text in the SPC:

	4.3 Contraindications • severe renal impairment (glomerular filtration rate < 30 ml/min) 4.9 Overdose Only in the case of severe renal insufficiency a cumulation of magnesium may arise in combination with a manifested intoxication. In general, plasma concentrations up to 2 mmol/l are well tolerated. Intoxication symptoms: blood pressure fall, nausea, vomiting, hyporeflexia, somnolence, changes in the electrocardiogram, respiratory depression and cardiac arrest. Intoxication therapy: Intravenous administration of calcium and slow intravenous administration of 0.5 – 2 mg neostigminmetilsulfat; intravenous and per-oral administration of isotonic sodium chloride solution; ventilatory and circulatory support; in case of renal insufficiency: haemodialysis.
Additional risk minimisation measure(s) (repeat as necessary)	NA

EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES

This is the first risk management plan for Magnesium Diasporal 400 mg direkt, therefore, the effectiveness of the risk minimisation activities cannot be evaluated yet. However as magnesium oxide and magnesium citrate are in well-established use and marketed in Europe since many years, routine risk minimisation activities are supposed to be appropriate for Magnesium Diasporal 400 mg direkt.

Effectiveness of risk minimization measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The safety profile and required risk measures are sufficiently discussed in the published literature provided. No further safety measures besides routine pharmacovigilance risk minimisation activities are deemed necessary.

Criteria for judging the success of the proposed risk minimisation measures	N/A
Planned dates for assessment	N/A
Impact of risk minimisation	N/A
Comment	

V.2 RISK MINIMISATION MEASURE FAILURE (IF APPLICABLE)

Not applicable

V.3 SUMMARY TABLE OF RISK MINIMISATION MEASURES

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Gastrointestinal disorders	Proposed text in the PL in section 4: "If you get any side effects, you should temporarily interrupt the treatment. After the symptoms improve and/or are eliminated you can restart treatment with a reduced dosage." .	NA
Important potential risk		
Side effects associated with increased plasma concentrations of magnesium due to severe renal impairment	Proposed text in the SPC: 4.3 Contraindications • severe renal impairment (glomerular filtration rate < 30 ml/min)	N/A

	4.9 Overdose Only in the case of severe renal insufficiency a cumulation of magnesium may arise in combination with a manifested intoxication. In general, plasma concentrations up to 2 mmol/l are well tolerated. Intoxication symptoms: blood pressure fall, nausea, vomiting, hyporeflexia, somnolence, changes in the electrocardiogram, respiratory depression and cardiac arrest. Intoxication therapy: Intravenous administration of calcium and slow intravenous administration of 0.5 – 2 mg neostigminmetilsulfat; intravenous and per-oral administration of isotonic sodium chloride solution; ventilatory and circulatory support; in case of renal insufficiency: haemodialysis.	

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Copy table from Part I: SVIII

Summary of safety concerns	
Important identified risks	Gastrointestinal adverse reactions
Important potential risks	Side effects associated with increased plasma concentration of magnesium due to severe renal impairment
Missing information	None

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable

VI.1.3 SUMMARY OF POST AUTHORISATION EFFICACY DEVELOPMENT PLAN

Not applicable

VI.1.4 SUMMARY TABLE OF RISK MINIMISATION MEASURES

Safety concern	**Routine risk minimisation activities sufficient?**	**If yes, provide description of routine activity and justification**
Important identified risk		
Gastrointestinal adverse reaction	yes	Magnesium oxide and magnesium citrate are active substances in well-established use. Important risks are adequately described in the product information. The safety profile and required risk measures are sufficiently discussed in the published literature provided. No further safety measures besides routine pharmacovigilance risk minimisation activities are deemed necessary.

Important potential risk		
Side effects associated with increased plasma concentrations of magnesium due to severe renal impairment	yes	Magnesium oxide and magnesium citrate are active substances in well-established use. Important risks are adequately described in the product information. The safety profile and required risk measures are sufficiently discussed in the published literature provided. No further safety measures besides routine pharmacovigilance risk minimisation activities are deemed necessary.
Important missing information		
None	N/A	N/A

VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of disease epidemiology

Magnesium Diasporal 400 mg direkt is indicated for treatment and prevention of magnesium deficiency. A magnesium deficiency occurs with different symptoms. Signs of magnesium deficiency include muscular symptoms (tingling sensation, twitch, tremor, muscle cramps), cardiac arrhythmias and neurological symptoms (dizziness, vertigo, fatigue).

Magnesium deficiency may occur because of reduced magnesium intake (unbalanced diet, fasting), increased magnesium loss (diarrhea, vomiting, intense sweating), diseases (diabetes, hereditary magnesium-losing disorders, inflammatory bowel disease). Also several drugs e.g. proton pump inhibitors to reduce gastric acid production, diuretics (water pills) for high blood pressure or aminoglycoside antibiotics for antibacterial treatment may lead to magnesium deficiency. Pregnancy, lactation and competitive sport represent situations of increased magnesium requirements.

Magnesium Diasporal 400 mg direkt is indicated in adults. The safety and efficacy of Magnesium Diasporal 400 mg direkt in children has not been established.

VI.2.2 SUMMARY OF TREATMENT BENEFITS

Magnesium supplementation is used to treat patients with magnesium deficiency. A 10 week old, female infant suffering from recurrent cramps was first treated with oral magnesium sulfate caused frequent loose stool and black staining of the teeth. Better compliance after switching

from magnesium sulfate to magnesium oxide resulted in an increase magnesium level in blood and the disappearance of the black staining of the teeth as well as frequent loose stool. The infant required an oral elemental magnesium dosage of 15 mg/kg/day to maintain adequate blood levels to keep her free from cramps. A further study demonstrated the effect of magnesium oxide supplementation on magnesium deficiency and correlating different symptoms (e.g. numbness and cramps in hands and feet) in a 39-old woman among other magnesium compounds (intravenous magnesium, followed by oral magnesium glycerophosphate). Blood magnesium level stabilized only after treatment with magnesium oxide 3 x 100 mg 9-times/day. After the diagnosis of severe magnesium deficiency as well as calcium deficiency, a 40 day-old female infant patient was discharged with different magnesium preparations (oral and intravenous). During a 4 years period, treatment was switched to oral magnesium citrate only because of absence of side effects and. The study shows that treatment with high doses of oral magnesium citrate is successful to keep a patient free from severe magnesium deficiency symptoms.

As magnesium deficiency can result in many clinical symptoms, magnesium is broadly used. Several diseases as well as special medical conditions such as migraine, diabetes, cramping, cardiovascular diseases, pregnancy, bone turnover, premenstrual syndrome and others are known to be in correlation with magnesium deficiency. Magnesium supplementation has also a positive effect on sleep and sport performance.Altogether, the results of different clinical trials revealed that administration of magnesium improves the medical condition of the subjects.

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

Not applicable.

VI.2.4 SUMMARY OF SAFETY CONCERNS

Overall, oral administration of magnesium oxide and magnesium citrate is safe and well tolerated in clinical studies as well as in daily practice, as the market observation constantly shows over years. All adverse drug reactions of magnesium oxide and magnesium citrate reported in identified literature were non-serious, and most of them were basically related diarrhoea or soft stool. The excellent safety profile of this product can result in good compliance.

Important identified risks

Risk	What is known	Preventability
Diarrhoea or soft stool.	Soft stool to diarrhoea may occur at the beginning of the treatment, which is harmless and will usually decrease in frequency as the treatment continues.	If any side effects occur, it is recommend to temporarily interrupt the treatment. After the symptoms improve and/or are eliminated treatment can be restarted with a reduced dosage.

Important potential risks

Risk	What is known
Side effects associated with increased plasma concentration of magnesium due to severe renal impairment	In the case of a normal renal function, magnesium toxication due to oral overdose of magnesium is not expected. Only in the case of severe renal impairment a magnesium intoxication may occure. Therefore the use of magnesium has to be avoided when renal function is severely limited.

Missing information

Risk	What is known
NA	

VI.2.5 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is

provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Magnesium Diasporal 400 Direkt can be found in the X's EPAR page.

This medicine has no additional risk minimisation measures.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk		
Gastrointestinal disorders	Routine pharmacovigilance activities are considered sufficient and no further actions are required.	Important identified risks are adequately described in the product information. No further risk management activities are necessary.
Important potential risk		
Side effects associated with increased plasma concentrations of magnesium due to severe renal impairment	Routine pharmacovigilance activities are considered sufficient and no further actions are required.	Important potential risks are adequately described in the product information. No further risk management activities are necessary.
Important missing information		
None	N/A	N/A

VI.2.6 PLANNED POST-AUTHORISATION DEVELOPMENT PLAN

Not applicable. No post-authorisation development is planned.

VI.2.7 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable. This is the first RMP for Magnesium Diasporal 400 mg direkt.

References

Abbasi B, Kimiagar M, Sadeghniiat K, Shirazi MM, Hedayati M, Rashidkhani B. The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. J Res Med Sci. 2012 Dec;17(12):1161-9.

Almoznino-Sarafian D, Berman S, Mor A, Shteinshnaider M, Gorelik O, Tzur I, Alon I, Modai D, Cohen N. Magnesium and C-reactive protein in heart failure: an anti-inflammatory effect of magnesium administration? Eur J Nutr 46(4), 230-237 (2007).

Almoznino-Sarafian D, Sarafian G, Berman S, Shteinshnaider M, Tzur I, Cohen N, Gorelik O. Magnesium administration may improve heart rate variability in patients with heart failure. Nutr Metab Cardiovasc Dis 19(9), 641-645 (2009).

Andoh TF, Burdmann EA, Fransechini N, Houghton DC, Bennett WM. Comparison of acute rapamycin nephrotoxicity with cyclosporine and FK506. Kidney Int 50(4), 1110-1117 (1996).

Ariceta G, Rodriguez-Soriano J, Vallo A, Navajas A. Acute and chronic effects of cisplatin therapy on renal magnesium homeostasis. Med Pediatr Oncol 28(1), 35-40 (1997).

Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 98(12), 1198-1204 (1998).

Aydin H, Deyneli O, Yavuz D, Gozu H, Mutlu N, Kaygusuz I, Akalin S. Short-term oral magnesium supplementation suppresses bone turnover in postmenopausal osteoporotic women. Biol Trace Elem Res 133(2), 136-143 (2010b).

Bagis S, Karabiber M, As I, Tamer L, Erdogan C, Atalay A. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? Rheumatol Int. 2013 Jan;33(1):167-72

Barton CH, Vaziri ND, Martin DC, Choi S, Alikhani S. Hypomagnesemia and renal magnesium wasting in renal transplant recipients receiving cyclosporine. Am J Med 83(4), 693-699 (1987).

Bearcroft CP, Domizio P, Mourad FH, Andre EA, Farthing MJ. Cisplatin impairs fluid and electrolyte absorption in rat small intestine: a role for 5-hydroxytryptamine. Gut 44(2), 174-179 (1999).

Bede O, Surányi A, Pintér K, Szlávik M, Gyurkovits K. Urinary magnesium excretion in asthmatic children receiving magnesium supplementation: a randomized, placebo-controlled, double-blind study. Magnes Res. 2003 Dec;16(4):262-70.

Bircan I, Turkkahraman D, Dursun O, Karaguzel G. Successful management of primary hypomagnesaemia with high-dose oral magnesium citrate: a case report. Acta Paediatr 95(12), 1697-1699 (2006).

Borrello G, Mastroroberto P, Curcio F, Chello M, Zofrea S, Mazza ML. The effects of magnesium oxide on mild essential hypertension and quality of life. Current Therapeutic Research Vol. 57, NO.10, October 1996

Brilla LR, Haley TF. Effect of magnesium supplementation on strength training in humans. J Am Coll Nutr. 1992 Jun;11(3):326-9

Cammu G. Interactions of neuromuscular blocking drugs. Acta Anaesthesiol Belg 52(4), 357-363 (2001).

Carpenter TO, DeLucia MC, Zhang JH, Bejnerowicz G, Tartamella L, Dziura J, Petersen KF, Befroy D, Cohen D. A randomized controlled study of effects of dietary magnesium oxide supplementation on bone mineral content in healthy girls. J Clin Endocrinol Metab. 2006 Dec;91(12):4866-72.

Cerklewski FL. Influence of dietary magnesium on fluoride bioavailability in the rat. J Nutr 117(3), 496-500 (1987).

Chacko SA, Sul J, Song Y, Li X, LeBlanc J, You Y, Butch A, Liu S. Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. Am J Clin Nutr 93(2), 463-473 (2011).

Chiuve SE, Korngold EC, Januzzi JL, Jr., Gantzer ML, Albert CM. Plasma and dietary magnesium and risk of sudden cardiac death in women. Am J Clin Nutr 93(2), 253-260 (2011).

Cundy, T. and Dissanayake, A. (2008) Severe hypomagnesaemia in long-term users of proton-pump inhibitors. Clin. Endocrinol. 69, 338–341

D'Almeida A, Carter JP, Anatol A, Prost C. Effects of a combination of evening primrose oil (gamma linolenic acid) and fish oil (eicosapentaenoic + docahexaenoic acid) versus magnesium, and versus placebo in preventing pre-eclampsia. Women Health. 1992;19(2-3):117-31.

De Lordes Lima M, Cruz T, Pousada JC, Rodrigues LE, Barbosa K, Canguçu V. The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. Diabetes Care. 1998 May;21(5):682-6.

Del Gobbo LC, Imamura F, Wu JH, de Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr. 2013 Jul;98(1):160-73

Djurhuus MS, Klitgaard NA, Pedersen KK. Effect of glucose/insulin infusion and magnesium supplementation on serum and muscle sodium and potassium and muscle [3H]ouabain binding capacity in Type 1 diabetes mellitus. Scand J Clin Lab Invest. 2003;63(2):93-102.

Dong JY, Xun P, He K, Qin LQ. Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. Diabetes Care 34(9), 2116-2122 (2011).

Dumont L, Lysakowski C, Tramer MR, Junod JD, Mardirosoff C, Tassonyi E, Kayser B. Magnesium for the prevention and treatment of acute mountain sickness. Clin Sci (Lond) 106(3), 269-277 (2004).

Durlach J. Present and future of magnesium research. Journal of Japanese Society for Magnesium Research 12(2), 113-135 (1993).

EFSA. Tolerable upper intake levels for vitamins and minerals. European Food Safety Authority (2006).

Efstratopoulos AD, Voyaki SM, Meikopoulos MA. Alterations of serum magnesium under chronic therapy with diuretics and/or angiotensin-converting enzyme inhibitors in hypertensive patients in Magnesium: current status and new developments (eds Theophanides T & Anastassopoulou) 209-214 (Kluwer Academic Publishers, 1997).

Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med 355(17), 1834-1836 (2006).

Fisher DM. Clinical pharmacology of neuromuscular blocking agents. Am J Health Syst Pharm 56(11 Suppl 1), S4-9 (1999).

Ford ES. Serum magnesium and ischaemic heart disease: findings from a national sample of US adults. Int J Epidemiol 28(4), 645-651 (1999).

Furlanetto, T.W. and Faulhaber, G. A. (2011) Hypomagnesemia and proton pump inhibitors: below the tip of the iceberg. Arch. Intern. Med. 171, 1391–1392

Fuentes JC, Salmon AA, Silver MA. Acute and chronic oral magnesium supplementation: effects on endothelial function, exercise capacity, and quality of life in patients with symptomatic heart failure. Congest Heart Fail. 2006 Jan-Feb;12(1):9-13

Gallelli L, Avenoso T, Falcone D, Palleria C, Peltrone F, Esposito M, De Sarro G, Carotenuto M, Guidetti V. Effects of acetaminophen and ibuprofen in children with migraine receiving preventive treatment with magnesium. Headache. 2014 Feb;54(2):313-24

Giapros VI, Andronikou S, Cholevas VI, Papadopoulou ZL. Renal function in premature infants during aminoglycoside therapy. Pediatr Nephrol 9(2), 163-166 (1995).

Gradon JD, Fricchione L, Sepkowitz D. Severe hypomagnesemia associated with pentamidine therapy. Rev Infect Dis 13(3), 511-512 (1991).

Grieff M, Bushinsky DA. Diuretics and disorders of calcium homeostasis. Semin Nephrol 31(6), 535-541 (2011).

Guasch-Ferré M, Bulló M, Estruch R, Corella D, Martínez-González MA, Ros E, Covas M, Arós F, Gómez-Gracia E, Fiol M, Lapetra J, Muñoz MÁ, Serra-Majem L, Babio N, Pintó X, Lamuela-Raventós RM, Ruiz-Gutiérrez V, Salas-Salvadó J; PREDIMED Study Group. Dietary magnesium intake is inversely associated with mortality in adults at high cardiovascular disease risk. J Nutr. 2014 Jan;144(1):55-60.

Hashimoto T, Hara A, Ohkubo T, Kikuya M, Shintani Y, Metoki H, Inoue R, Asayama K, Kanno A, Nakashita M, Terata S, Obara T, Hirose T, Hoshi H, Totsune K, Satoh H, Imai Y. Serum magnesium, ambulatory blood pressure, and carotid artery alteration: the Ohasama study. Am J Hypertens 23(12), 1292-1298 (2010).

Hashizume N, Mori M. An analysis of hypermagnesemia and hypomagnesemia. Jpn J Med 29(4), 368-372 (1990).

Hattori K, Saito K, Sano H, Fukuzaki H. Intracellular magnesium deficiency and effect of oral magnesium on blood pressure and red cell sodium transport in diuretic-treated hypertensive patients. Jpn Circ J. 1988 Nov;52(11):1249-56.

Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R (2010) A Case Series of Proton Pump Inhibitor-Induced Hypomagnesemia. Am J Kidney Dis. 2010 (Epub ahead of print)

Hornyak M, Voderholzer U, Hohagen F, Berger M, Riemann D. Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. Sleep. 1998 Aug 1;21(5):501-5.

Huycke MM, Naguib MT, Stroemmel MM, Blick K, Monti K, Martin-Munley S, Kaufman C. A double-blind placebo-controlled crossover trial of intravenous magnesium sulfate for foscarnet-induced ionized hypocalcemia and hypomagnesemia in patients with AIDS and cytomegalovirus infection. Antimicrob Agents Chemother 44(8), 2143-2148 (2000).

Jaipakdee S, Prasongwatana V, Premgamone A, Reungjui S, Tosukhowong P, Tungsanga K, Suwantrai S, Noppawinyoowong C, Maskasame S, Sriboonlue P. The effects of potassium and magnesium supplementations on urinary risk factors of renal stone patients. J Med Assoc Thai 87(3), 255-263 (2004).

Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med 159(18), 2151-2159 (1999).

Kass LS, Skinner P, Poeira F. A pilot study on the effects of magnesium supplementation with high and low habitual dietary magnesium intake on resting and recovery from aerobic and resistance exercise and systolic blood pressure. J Sports Sci Med. 2013 Mar 1;12(1):144-50.

Kawano Y, Matsuoka H, Takishita S, Omae T. Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. Hypertension. 1998 Aug;32(2):260-5.

Koseoglu E, Talaslioglu A, Gonul AS, Kula M. The effects of magnesium prophylaxis in migraine without aura. Magnes Res 21(2), 101-108 (2008).

Kuipers, M. T., Thang, H. D. and Arntzenius, A. B. (2009) Hypomagnesaemia due to use of proton pump inhibitors: a review. Neth. J. Med. 67, 169–172

Kurata Y, Tamano S, Shibata M-A, Hagiwara A, Fukushima S, Ito N. Lack of carcinogenicity of magnesium chloride in a long-term feeding study in B6C3F1 mice. Food and Chemical Toxicology 27(9), 559-563 (1989).

Lajer H, Daugaard G. Cisplatin and hypomagnesemia. Cancer Treat Rev 25(1), 47-58 (1999).

Lal J, Vasudev K, Kela AK, Jain SK. Effect of oral magnesium supplementation on the lipid profile and blood glucose of patients with type 2 diabetes mellitus. J Assoc Physicians India. 2003 Jan;51:37-42.

Lameris AL, Monnens LA, Bindels RJ, Hoenderop JG. Drug-induced alterations in Mg2+ homoeostasis. Clin Sci (Lond) 123(1), 1-14 (2012).

Laniado-Laborin R, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. Rev Iberoam Micol 26(4), 223-227 (2009).

Larsson SC, Orsini N, Wolk A. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. Am J Clin Nutr. 2012 Feb;95(2):362-6.

Lee S, Park HK, Son SP, Lee CW, Kim IJ, Kim HJ. Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normo-magnesemic nondiabetic overweight Korean adults. Nutr Metab Cardiovasc Dis. 2009 Dec;19(11):781-8.

Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE, Hu FB. Magnesium intake and risk of type 2 diabetes in men and women. Diabetes Care 27(1), 134-140 (2004).

Lutsey PL, Alonso A, Michos ED, Loehr LR, Astor BC, Coresh J, Folsom AR. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr. 2014 Sep;100(3):756-64

Mani S. Pentamidine-induced renal magnesium wasting. Aids 6(6), 594-595 (1992).

Möhnle P, Goetz AE. Physiologische Effekte, Pharmakologie und Indikationen zur Gabe von Magnesium. Anaesthesist 50(337-389 (2001).

Mordes JP, Wacker WE. Excess magnesium. Pharmacol Rev 29(273-300 (1977).

Motoyama T, Sano H, Fukuzaki H. Oral magnesium supplementation in patients with essential hypertension. Hypertension. 1989 Mar;13(3):227-32.

Nielsen FH, Johnson LK, Zeng H. Magnesium supplementation improves indicators of low magnesium status and inflammatory stress in adults older than 51 years with poor quality sleep. Magnes Res 23(4), 158-168 (2010).

Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest 115(6), 1651-1658 (2005).

Ogawa R, Echizen H. Clinically significant drug interactions with antacids: an update. Drugs 71(14), 1839-1864 (2011).

Peacock JM, Ohira T, Post W, Sotoodehnia N, Rosamond W, Folsom AR. Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 160(3), 464-470 (2010).

Peikert A, Wilimzig C, Kohne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia 16(4), 257-263 (1996).

Pokan R, Hofmann P, von Duvillard SP, Smekal G, Wonisch M, Lettner K, Schmid P, Shechter M, Silver B, Bachl N. Oral magnesium therapy, exercise heart rate, exercise tolerance, and myocardial function in coronary artery disease patients. Br J Sports Med 40(9), 773-778 (2006).

Qu X, Jin F, Hao Y, Li H, Tang T, Wang H, Yan W, Dai K. Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies. PLoS One. 2013;8(3):e57720.

Quamme GA, de Rouffignac C. Epithelial magnesium transport and regulation by the kidney. Front Biosci 5(D694-711 (2000).

Reffelmann T, Ittermann T, Dorr M, Volzke H, Reinthaler M, Petersmann A, Felix SB. Low serum magnesium concentrations predict cardiovascular and all-cause mortality. Atherosclerosis 219(1), 280-284 (2011).

Ridgway LE 3rd, Muise K, Wright JW, Patterson RM, Newton ER. A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis. Am J Obstet Gynecol. 1990 Sep;163(3):879-82.

Roffe C, Sills S, Crome P, Jones P. Randomised, cross-over, placebo controlled trial of magnesium citrate in the treatment of chronic persistent leg cramps. Med Sci Monit 8(5), CR326-330 (2002).

Ross JR, Dargan PI, Jones AL, Kostrzewski A. A case of hypomagnesaemia due to malabsorption, unresponsive to oral administration of magnesium glycerophosphate, but responsive to oral magnesium oxide supplementation. Gut. 2001 Jun;48(6):857-8.

Sanjuliani AF, de Abreu Fagundes VG, Francischetti EA. Effects of magnesium on blood pressure and intracellular ion levels of Brazilian hypertensive patients. Int J Cardiol. 1996 Oct 11;56(2):177-83.

Sawai J., Kojima H., Kano F., Igarashi H., Hashimoto A., Kawada E., Kokugan T., Shimizu M. Short Communication: Ames assay with Salmonella typhimurium TA102 for mutagenicity and antimutagenicity of metallic oxide powders having antibacterial activities. World Journal of Microbiology & Biotechnology 14, 773-775 (1998).

Schulze MB, Schulz M, Heidemann C, Schienkiewitz A, Hoffmann K, Boeing H. Fiber and magnesium intake and incidence of type 2 diabetes: a prospective study and meta-analysis. Arch Intern Med 167(9), 956-965 (2007).

Scoble JE, Freestone A, Varghese Z, Fernando ON, Sweny P, Moorhead JF. Cyclosporin-induced renal magnesium leak in renal transplant patients. Nephrol Dial Transplant 5(9), 812-815 (1990).

Setaro L, Santos-Silva PR, Nakano EY, Sales CH, Nunes N, Greve JM, Colli C. Magnesium status and the physical performance of volleyball players: effects of magnesium supplementation. J Sports Sci. 2014;32(5):438-45.

Shah GM, Kirschenbaum MA. Renal magnesium wasting associated with therapeutic agents. Miner Electrolyte Metab 17(1), 58-64 (1991).

Shechter M, Merz CN, Paul-Labrador M, Meisel SR, Rude RK, Molloy MD, Dwyer JH, Shah PK, Kaul S. Beneficial antithrombotic effects of the association of pharmacological oral magnesium therapy with aspirin in coronary heart disease patients. Magnes Res. 2000 Dec;13(4):275-84.

Shechter M, Sharir M, Labrador MJ, Forrester J, Silver B, Bairey Merz CN. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation. 2000 Nov 7;102(19):2353-8.

Shechter M, Bairey Merz CN, Stuehlinger HG, Slany J, Pachinger O, Rabinowitz B. Effects of oral magnesium therapy on exercise tolerance, exercise-induced chest pain, and quality of life in patients with coronary artery disease. Am J Cardiol 91(5), 517-521 (2003).

Simmons D, Joshi S, Shaw J. Hypomagnesaemia is associated with diabetes: Not pre-diabetes, obesity or the metabolic syndrome. Diabetes Res Clin Pract 87(2), 261-266 (2010).

Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. Diabet Med 23(10), 1050-1056 (2006).

Spätling L, Classen HG, Külpmann WR, Manz F, Rob PM, Schimatschek HF, Vierling W, Vormann J, Weigert A, Wink K. Diagnostik des Magnesiummangels. Aktuelle Empfehlungen der Gesellschaft für Magnesium-Mangel e.V. Fortschr Med Orig 118(Suppl 2), 49-53 (2000).

Stünzi H, Perrin DD. Stability constants of metal complexes of phosphonoacetic acid. Journal of Inorganic Biochemistry 10(4), 309-316 (1979).

Swaminathan R. Magnesium metabolism and its disorders. Clin Biochem Rev 24(2), 47-66 (2003).

Takizawa T, Yasuhara K, Mitsumori K, Onodera H, Koujitani T, Tamura T, Takagi H, Hirose M. A 90-day repreated dose oral toxicity study of magnesium chloride in F344 rats.

Kokuritsu Iyakuhin Shokuhin Eisei Kenkyujo Hokoku = Bulletin of National Institute of Health Sciences 118(63-70 (2000).

Tanaka H, Hagiwara A, Kurata Y, Ogiso T, Futakuchi M, Ito N. Thirteen-week oral toxicity study of magnesium chloride in B6C3F1 mice. Toxicol Lett 73(1), 25-32 (1994).

Tarighat Esfanjani A, Mahdavi R, Ebrahimi Mameghani M, Talebi M, Nikniaz Z, Safaiyan A. The effects of magnesium, L-carnitine, and concurrent magnesium-L-carnitine supplementation in migraine prophylaxis. Biol Trace Elem Res. 2012 Dec;150(1-3):42-8.

Tejpar S, Piessevaux H, Claes K, Piront P, Hoenderop JG, Verslype C, Van Cutsem E. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. Lancet Oncol 8(5), 387-394 (2007).

Thebault S, Alexander RT, Tiel Groenestege WM, Hoenderop JG, Bindels RJ. EGF increases TRPM6 activity and surface expression. J Am Soc Nephrol 20(1), 78-85 (2009).

Tong GM, Rude RK. Magnesium deficiency in critical illness. J Intensive Care Med 20(1), 3-17 (2005).

Unachak K, Louthrenoo O, Katanyuwong K. Primary hypomagnesemia in Thai infants: a case report with 7 years follow-up and review of literature. J Med Assoc Thai. 2002 Nov;85(11):1226-31.

Van Laecke S, Nagler EV, Taes Y, Van Biesen W, Peeters P, Vanholder R. The effect of magnesium supplements on early post-transplantation glucose metabolism: a randomized controlled trial. Transpl Int. 2014 Sep;27(9):895-902.

Veronese N, Berton L, Carraro S, Bolzetta F, De Rui M, Perissinotto E, Toffanello ED, Bano G, Pizzato S, Miotto F, Coin A, Manzato E, Sergi G. Effect of oral magnesium supplementation on physical performance in healthy elderly women involved in a weekly exercise program: a randomized controlled trial. Am J Clin Nutr. 2014 Sep;100(3):974-81.

Villegas R, Gao YT, Dai Q, Yang G, Cai H, Li H, Zheng W, Shu XO. Dietary calcium and magnesium intakes and the risk of type 2 diabetes: the Shanghai Women's Health Study. Am J Clin Nutr 89(4), 1059-1067 (2009).

Vormann J. Magnesium - an important mineral in prevention and therapy. Ernährungsumschau 55(726-731 (2008).

Walker AF, De Souza MC, Vickers MF, Abeyasekera S, Collins ML, Trinca LA. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. J Womens Health. 1998 Nov;7(9):1157-65.

Wang F, Van Den Eeden SK, Ackerson LM, Salk SE, Reince RH, Elin R Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial.J. Headache. 2003 Jun;43(6):601-10.

Woods KL. Possible pharmacological actions of magnesium in acute myocardial infarction. Br J Clin Pharmacol 32(1), 3-10 (1991).

Willimzig C, Pannewig K. Protina Plc 85737 Ismaning. High-dose oral magnesium therapy in pregnancy. Der Allgemeinarzt (General Practitioner) 18/100994

PART VII: ANNEXES

List of annexes

Annex No		
1	Interface between EU-RMP and EudraVigilance/EPITT	N/A
2	Proposed SPC, Package leaflet	enclosed
3	Worldwide marketing authorisation status by country	N/A
4	Synopsis of ongoing and completed clinical trial programme	N/A
5	Synopsis of ongoing and completed pharmacoepidemiological study programme	N/A
6	Protocols for proposed and ongoing studies in RMP part III	N/A
7	Specific adverse event follow-up forms	N/A
8	Protocols for proposed and ongoing studies in RMP part IV	N/A
9	Synopsis of newly available study reports for RMP parts III-IV	N/A
10	Details of proposed additional risk minimisation activities	N/A
11	Mock up examples in English of the material provided to healthcare professionals and patients	N/A
12	Other supporting data	N/A

Annex 1: EudraVigilance Interface

Not applicable.

Annex 2: Proposed SPC, package leaflet

SUMMARY OF PRODUCT CHARACTERISTICS

[Nationally approved name] 400 mg granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet (2.22 g) contains magnesium hydrogencitrate 647.06 mg and magnesium oxide, heavy 572.10 mg corresponding to 400 mg magnesium.

Excipient with known effect:
929.44 mg sorbitol (E420) per sachet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules in sachet

Orange granules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prevention of magnesium deficiency in adults.

4.2 Posology and method of administration

Posology
Adults
1 sachet of granules daily (400 mg magnesium).

Paediatric population
The safety and efficacy of [Nationally approved name] 400 mg granules in children and adolescents has not been established.

Renal impairment:
[Nationally approved name] 400 mg granules is contraindicated in patients with severe renal impairment (see section 4.3).

Method of administration
For oral use.
[Nationally approved name] 400 mg granules should be taken directly into the mouth onto the tongue and swallowed without water shortly before a meal.

Duration of treatment
The duration of treatment depends on the extent of the magnesium deficiency and should be decided by a doctor. Safety data for comparable magnesium preparations are available from clinical studies from 4 weeks to 6 month.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- severe renal impairment (glomerular filtration rate < 30 ml/min)
- conduction disorders of the heart that cause slow heartbeat (bradycardia)

4.4 Special warnings and special precautions for use

This medicinal product contains sorbitol (E 420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

If an undesirable effect occurs, the therapy should be temporarily interrupted and can be adjusted after improvement and/or elimination of the symptoms by reducing the dosage.

4.5 Interaction with other medicinal products and other forms of interaction

As magnesium and other medicinal products may mutually influence each other's absorption, a time interval of 2 to 3 hours should generally be respected if possible.

This specifically applies to fluorides and tetracycline for which a time interval of 2 to 3 hours should be strictly respected.

Aminoglycoside antibiotics, cisplatinum and cyclosporin A accelerate the secretion of magnesium. Diuretics (such as thiazide and furosemide), EGF-receptor antagonists (such as cetuximab and erlotinib), proton pump inhibitors (such as omeprazole and pantoprazole), viral DNA polymerases-inhibiting

foscarnet, pentamidine, rapamycin and amphotericin B may cause magnesium deficiency. Because of increased magnesium losses, a dose adjustment of magnesium may be necessary when taking the above mentioned substances.

4.6 Fertility, pregnancy and lactation

Pregnancy
[Nationally approved name] 400 mg granules can be used during pregnancy. There are no indications of any risk of malformation. However, there is little documented experience in humans with regard to use in early pregnancy.

Lactation
[Nationally approved name] 400 mg granules can be used during breast-feeding. Magnesium citrate/metabolites and/or magnesium oxide /metabolites are excreted in human milk, but at therapeutic doses of [Nationally approved name] 400 mg granules, no effects on the breastfed newborns/infants are anticipated.

Fertility
Based on the long-term experience, no effects of magnesium citrate and/or magnesium oxide on male and female fertility are anticipated.

4.7 Effects on ability to drive and use machines

[Nationally approved name] 400 mg granules has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Gastrointestinal disorders
Uncommon: soften faeces or diarrhoea at the beginning of the treatment (harmless and transitory).

For measures in case of the occurrence of an undesirable effect please see section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the case of intact renal function, magnesium toxication due to oral overdose of magnesium is not expected. Only in the case of severe renal insufficiency a cumulation of magnesium may arise in combination with a manifested intoxication.

In general, plasma concentrations up to 2 mmol/l are well tolerated.

Intoxication symptoms:
blood pressure fall, nausea, vomiting, hyporeflexia, somnolence, changes in the electrocardiogram, respiratory depression and cardiac arrest.

Intoxication therapy:
Intravenous administration of calcium and slow intravenous administration of 0.5 – 2 mg neostigminmetilsulfat;
intravenous and per-oral administration of isotonic sodium chloride solution;
ventilatory and circulatory support;
in case of renal insufficiency: haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary Tract and Metabolism, Other Mineral Supplements, magnesium (different salts in combination)
ATC code: A12CC30

Magnesium
- acts as a physiological calcium antagonist.
- stabilizes the phospholipids of the cell membrane.
- inhibits neuromuscular transmission.

5.2 Pharmacokinetic properties

Absorption

Magnesium is slowly and incompletely absorbed – primarily in the small bowel. Absorption rate depends on magnesium status and can be up to 70% in the case of a magnesium deficiency. It also depends on other factors including damage to the bowel mucosa, bowel motility, transit time, and physiological intestinal flora. The non-absorbable portion can produce a laxative effect.

Distribution to organs and tissue
The classical method of determining bioavailability using plasma concentration curves cannot be applied to magnesium.

The blood serum only contains approximately 1% of the overall depot of magnesium, i. e. 0.8 to 1.0 mmol/l (corresponds to 1.6 to 2.0 meq/l). Approximately 45 % of this depot are albumin-bound or bound to other ligands. The remaining ionised magnesium constitutes the physiologically active portion. Approximately half of the overall depot of magnesium is localised inside the cells. The remaining concentration of magnesium is contained in the bones. The portion adsorbed at the surface is in equilibrium with the magnesium contained in the blood serum.
Therefore, serum magnesium levels in the normal range (0.8 – 1.0 mmol/l) do not exclude magnesium deficiency as magnesium can also be released from intracellular stores into the blood under stressful conditions (e.g. blood sampling). Clinical symptoms of magnesium deficiency (muscular or neurological symptoms) as well as risk factors for magnesium deficits (see paragraphs below) must be considered.
Signs of magnesium deficiency include muscular symptoms (tingling sensation, twitch, muscle cramps) and neurological symptoms (nervousness, agitation, fatigue).

Elimination
Absorbed magnesium is practically only secreted via the kidney. The amount of renal reabsorption is generally between 95 and 100%, thereby regulating magnesium balance.

Magnesium homeostasis influenced by medication
Other drugs may inhibit intestinal absorption or increase renal excretion of magnesium (see section 4.5).

Magnesium homeostasis influenced by medical conditions
Excessive excretion of magnesium into the urine is a cause of magnesium depletion. Osmotic diuresis due to glucosuria (e.g in diabetic patients) can result in magnesium depletion. Therefore, diabetics have an increased requirement for magnesium.

Increased loss of magnesium or reduced absorption or reduced magnesium blood levels can be observed in other conditions e.g.: migraine, chronic inflammatory bowel diseases, , hyperthyroidism, patients with renal salt-losing syndrome, alcohol abuse, pregnancy.

5.3 Preclinical safety data

There are no studies available for magnesium hydrogencitrate or mangnesium oxid. Non-clinical data with different magnesium salts reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. There was no research carried out into genotoxicity, carcinogenic potential as well as toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Orange fruit powder
Iron oxide (E172)
Calcium stearate
Orange flavour
Orange juice flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sachets
Laminated foil (Paper/Aluminium/Polyethylene-Copolymer).
20, 50 or 100 sachets per 2.22 g granules.

Multipacks containing 200 sachets per 2.22 g granules (10 packs of 20 or 4 packs of 50 or 2 packs of 100, which must not be sold separately).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Protina Pharmazeutische Gesellschaft mbH
Adalperostraße 37
85737 Ismaning
Germany

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Package leaflet: Information for the user

[Nationally approved name] 400 mg granules

Magnesium

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You must talk to a doctor if you do not feel better or if you feel worse after 1 month.

What is in this leaflet

1. What [Nationally approved name] 400 mg granules is and what it is used for

[Nationally approved name] is a mineral preparation and contains the active ingredients magnesium hydrogencitrate and magnesium oxide, heavy.

[Nationally approved name] 400 mg granules is used in the treatment and prevention of magnesium deficiency in adults.

Magnesium deficiency may occur because of
- reduced magnesium intake, e. g. unbalanced diet or reduced food intake in elderly
- increased magnesium requirements like stress, intense sweating, competitive sport, pregnancy and lactation.

Magnesium deficiency may result in muscular symptoms (e.g. muscle cramps).

2. What you need to know before you take [Nationally approved name] 400 mg granules

Do not take [Nationally approved name] 400 mg granules:
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)
- if you have severe renal impairment (glomerular filtration rate < 30 ml / min)
- if you have conduction disorders of the heart that cause slow heartbeat (bradycardia)

Warnings and precautions
It is recommended to talk to your doctor or pharmacist before taking [Nationally approved name] 400 mg granules.

Children and adolescents
There is no experience of treating children and adolescents.

Other medicines and [Nationally approved name] 400 mg granules
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

You should avoid taking other medicines at the same time if possible. Allow 2 to 3 hours between taking [Nationally approved name] 400 mg granules and your other medicines to reduce the possibility of interaction.
- In the case of **fluorides** and **tetracycline** the time interval of 2-3 hours should be **strictly** respected.
- antibacterial antibiotics (aminoglycoside antibiotics), substances elevating urination (thiazide, furosemide) and substances blocking the production of stomach acid (omeprazole, pantoprazole) as well as the active substances cisplatinum, cyclosporin A, foscarnet, cetuximab, erlotinib, pentamidine, rapamycin and amphotericin B may cause magnesium deficiency. Ask your doctor if you need to adjust your daily dose of magnesium.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

[Nationally approved name] 400 mg granules can be used during pregnancy and during breast-feeding without concerns.
Based on long-term experience, no effects of magnesium hydrogencitrate and/or magnesium oxide on male and female fertility are anticipated.

Driving and using machines
[Nationally approved name] 400 mg granules has no or negligible influence on the ability to drive and use machines.

[Nationally approved name] 400 mg granules contains sorbitol
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take [Nationally approved name] 400 mg granules

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Renal impairment
The use of magnesium has to be avoided when renal function is severely limited.

The recommended dose is
Adults
1 sachet daily.
1 sachet of [Nationally approved name] 400 mg granules corresponds to a daily dose of 400 mg magnesium.

Paediatric population
Children and adolescents aged less than 18 years should receive magnesium preparations with a reduced amount of magnesium.

Method and route of administration
[Nationally approved name] 400 mg granules is for oral use only. The granules should be taken directly into the mouth onto the tongue and swallowed without water shortly before a meal.
If required, water may be taken after swallowing.

If you take more [Nationally approved name] 400 mg granules than you should
No side effects are expected, if your kidneys work properly. Any excessive amount of magnesium will be excreted through your kidneys.

Duration of treatment
The duration of treatment depends on the extent of the magnesium deficiency and should be decided by a doctor.

If you have taken more of this medicine than directed, or if a person accidentally has taken this medicine although it is not indicated (see section 2), please contact your doctor or pharmacist for judgment of the risk and advice.

If you forget to take [Nationally approved name] 400 mg granules
Do not take a double dose to make up for a forgotten dose.

If you have any further question on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Uncommon (may affect up to 1 in 100 people):
Soft stool to diarrhoea at the beginning of treatment (harmless and will usually decrease in frequency as the treatment continues).

If you get any side effects, you should temporarily interrupt the treatment. After the symptoms improve and/or are eliminated you can restart treatment with a reduced dosage.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V]. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store [Nationally approved name] 400 mg granules

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the sachet. The expiry date refers to the last day of that month.

6. Content of the pack and other information

What [Nationally approved name] 400 mg granules contains
- The active substances are magnesium hydrogencitrate and magnesium oxide, heavy. One sachet (2.22 g) contains magnesium hydrogencitrate 647.06 mg and magnesium oxide, heavy 572.10 mg corresponding to 400 mg magnesium.
- The other ingredients are sorbitol (E420), iron oxide (E172), calcium stearate, orange fruit powder, orange flavour, orange juice flavour

What [Nationally approved name] 400 mg granules looks like and content of the packs
Orange granules in sachets.
[Nationally approved name] 400 mg granules is available in packs containing 20, 50, or 100 sachets per 2.22 g granules or in multipacks containing 200 sachets per 2.22 g granules (10 packs of 20 sachets or 4 packs of 50 sachets or 2 packs of 100 sachets, which must not be sold separately).
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Protina Pharmazeutische Gesellschaft mbH
Adalperostraße 37
85737 Ismaning
Germany

This medicinal product is authorised in the Member States of the European Economic Area (EEA) under the following names:

Austria	To be completed nationally
Finland	To be completed nationally
Germany	To be completed nationally
Lithuania	To be completed nationally
Slovenia	To be completed nationally

This leaflet was last revised in {month YYYY}.

Annex 3: Worldwide marketing authorisation status by country (including EEA)

Not applicable.

Annex 4: Synopsis of ongoing and completed clinical trial programme

Not applicable.

Annex 5: Synopsis of ongoing and completed pharmacoepidemiological study programme

Not applicable.

Annex 6: Protocols for proposed and ongoing studies in categories 1-3 of the section “Summary table of additional phramacovigilance activities” in RMP part III

Not applicable.

Annex 7: Specific adverse event follow-up forms

Not applicable.

Annex 8: Protocols for proposed and ongoing studies in RMP part IV

Not applicable.

Annex 9: Newly available study reports for RMP Parts III &IV

Not applicable.

Annex 10: Details of proposed additional risk minimisation measures (if applicable)

Not applicable.

Annex 11: Mock-up of proposed additional risk minimisation measures (if applicable)

Not applicable.

Annex 12: Other supporting data (including referenced material)

Not applicable.