Development Safety Update Report
Report Number: 2

Trial Title: ***EFFECTS OF BENFOTIAMINE ON INTRAEPIDERMAL NERVE FIBER DENSITY (IENFD) AND DIABETIC NEUROPATHY IN SUBJECTS WITH SENSORIMOTOR DIABETIC POLYNEUROPATHY: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP PILOT STUDY OVER 12 MONTHS***

Reporting Period: 02 December 2014 – 22 October 2015

Investigational drug(s)	Benfotiamine
EudraCT number(s):	2013-001058-85
Sponsor	Wörwag Pharma GmbH & Co. KG
Address of Sponsor	Calwer Str. 7 71034 Böblingen Germany
Contact for this DSUR:	Dr. Rudite Klesmite QPPV Wörwag Pharma e-mail: dso@woerwagpharma.com
Signature of QPPV:	

The data contained in this report are confidential.

This DSUR includes unblinded information.

EXECUTIVE SUMMARY

- This is the 2nd DSUR for benfotiamine, summarising safety data received by Wörwag Pharma from 02 December 2014 – 22 October 2015 for the following study.
- The study was investigating **the effects of benfotiamine on intraepidermal nerve fiber density (IENFD) and diabetic neuropathy in patients with sensorimotor diabetic polyneuropathy and** was performed from September 2013 to September 2015:

  Study design: This is a mono-centric, randomized, placebo-controlled, double blind, parallel group pilot study over 12 months.

  Number of subjects: 22 patients with T1DM or T2DM and diabetic sensorimotor neuropathy were randomized ensuring 18 completers (at least 9 in each group) at 6 months and 11 completers at 12 months.

  The primary parameters of the trial were: Changes from baseline in intra-epidermal nerve fiber density (IENFD) after 6 and 12 months of benfotiamine/placebo treatment, respectively. For IENFD-measurement skin biopsies were scheduled at baseline, 6 and 12 months. Biopsies were analysed in three independent laboratories. None of these were able to detect nerve fibres in the biopsies. Therefore it was decided to terminate the study prematurely on 07 September 2015 for ethical reasons in order not to expose participants to further skin biopsies. Last patient visit was defined on 22-Oct-2015.
- Benfotiamine is a synthetic S-acyl derivative of thiamine (vitamin B1). It is indicated for the treatment or prophylaxis of vitamin B1 deficiency conditions, if these cannot be resolved by dietary means and for the treatment of neuropathies and cardiovascular disorders that are caused by vitamin B1 deficiency. Benfotiamine was given orally 600 mg/day for 3 months followed by benfotiamine 300 mg/day for the rest of the study duration.
- The product (*milgamma protekt film-coated tablets*) obtained its first authorisation in Germany in 2005 and is currently authorised in 15 countries.
- A small number of possible adverse reactions have been identified following analysis of the reporting period of the respective study with benfotiamine.

  There have been 4 AEs in 4 patients during the reporting period (see chapter 8.1)

  As of the data at data lock point (22/10/2015), 3 case reports corresponding to 7 SAEs have been reported **cumulatively**. The trial safety profile remains unchanged and is in line with the current information available in the SmPC.
- Based on the presented data, there are no newly identified risks for benfotiamine or the product *milgamma protekt film-coated tablets.*

  Evaluation of the available data has not revealed any gaps in the knowledge about the product.

- There were no actions taken for safety reasons including significant changes to the reference product information.
- Based on the evaluation of the cumulative safety data and the benefit-risk analysis, no changes to the reference safety information or new risk minimisation activities are deemed necessary at this time.

  Accordingly, benfotiamine and *milgamma protekt film-coated tablets* continue to be considered a safe and effective medicinal product with a positive benefit-risk ratio.

TABLE OF CONTENTS

1. INTRODUCTION

This is the 2nd Development Safety Update Report (DSUR) for benfotiamine summarising safety data received by Wörwag Pharma from 02.12.2014 to 22.10.2015. This report covers a single clinical trial. The Clinical Trial was approved on 30.07.2013 and this is the Development International Birth Date.

Benfotiamine, a prodrug of thiamin (vitamin B1) with a high bioavailability, was shown to block in vitro 4 pathomechanisms that lead to the development of diabetic complications (the polyol pathway, the hexosamine pathway, the protein kinase C pathway and the formation of advanced glycation end products -AGEs) [2][3] and to have direct antioxidant properties [4]. Studies in animal models have sustained this concept showing that benfotiamine positively influences nerve structure and function in diabetes [5]. Moreover, benfotiamine was shown to improve endothelial function in people with diabetes and healthy smokers [6][7]. Several studies with a duration of maximal 3 months have demonstrated that benfotiamine alone or in combination with vitamin B6 and B12 alleviates symptoms and deficits of DSP [1][8][9][10]. Fraser et al. [11] have shown no effects of benfotiamine given over 2 years at doses of 300 mg/day on nerve conduction studies, but the study design was criticized by Ziegler et al. [12] therefore these data have to be interpreted with caution. Except for one study by Stracke et al. [8] demonstrating that benfotiamine in combination with vitamin B6 and B12 improves nerve conduction velocity, no study in humans exists demonstrating that benfotiamine acts pathogenetically against the development of DSP and not only alleviates symptoms. But this would be important information since there is a scarcity of pathogenetically oriented therapies against DSP.

Moreover, it has been demonstrated that patients with T1DM and T2DM have a marked decrease in plasma thiamine concentrations due to an increased renal clearance of thiamine [13]. Diuretic therapy itself decreases thiamine loss in healthy subjects [14] and subjects with heart failure [15]. But it remained a matter of debate if thiamine (or benfotiamine) substitution should be recommended in the broad population of subjects with diabetes mellitus.

Skin biopsy (SB) is a minimally invasive method that allows a direct quantification of intra-epidermal nerve fiber density (IENFD, a morphological parameter) and allows for a sensitive quantification of diabetic neuropathy. Indeed, it has been shown that IENFD decreases early in the development of diabetic neuropathy [16][17]. Moreover, the IENFD was shown to improve within 1 year of lifestyle change in subjects with impaired glucose tolerance [17]. Therefore, the IENFD represents an optimal parameter to mirror structural nerve improvement following an intervention.

Skin autofluorescence (SAF) is a fast, non-invasive method for the assessment of skin AGEs [18]. Benfotiamine was suggested to decrease endogenous AGE production [2] and is supposed to reduce tissue AGE accumulation in vivo.

The aim of the present study is therefore to assess before, as well as 6 and 12 months following a therapy with benfotiamine the influence of therapy on IENFD, SAF, neuropathic symptoms and deficits in people with type 1 or 2 diabetes mellitus and DSP.

2. WORLDWIDE MARKETING APPROVAL STATUS

Trade name	Country	Date of authorisation	Last Renewal Date	Marketing authorisation number	Comments
Milgamma protekt	Armenia	2015-07-16	-	N 14718	-
Milgamma protekt	Azerbaijan	2015-10-30	-	DV No. 15-01013	-
milgamma mono 300	Republic of Belarus	2011-03-01	pending	9626/11	-
Milgamma protekt	Bulgaria	2012-09-24	-	20120474	-
milgamma mono 300	Germany	2005-06-23	2005-06-23	6366617.00.00	-
milgamma protekt	Germany	2005-06-23	2005-06-23	6366586.00.00	-
Benfogamma	Estonia	2015-01-28	-	864115	-
milgamma mono 300	Georgia	2010-07-13		R-002757	-
Benfogamma 300 mg filmtabletta	Hungary	2012-03-08	-	OGYI-T-22057/01-04	-
Milgamma Mono 300	Republic of Kazakh-stan	2011-11-07	pending	РК-ЛС -5 № 018403 / КР-ДЗ –5 № 018403	-
Benfogamma 300	Lithuania	2011-09-07	pending	LT/1/11/2583/001 -004	-
Benfogamma 300 mg apvalkotās tabletes	Latvia	2014-09-10	-	14-0186	-
Milgamma protekt	Moldova	2013-02-28	-	18857	-
Benfotiamin Worwag Pharma 300 mg filmsko obložene tablete	Slovenia	2013-04-10	-	H/13/00264/001	

Trade name	Country	Date of authorisation	Last Renewal Date	Marketing authorisation number	Comments
Benfogamma 300	Republic of Slovakia	2011-02-15	-	86/0089/11-S	--
Benfogamma 300	Ukraine	2011-01-28	pending	UA/11334/01/01	-

3. ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

During the period under review (i.e. from 02/12/2014 to 22/10/2015) no new information with a possible influence on the benefit-risk-balance of *milgamma protekt film-coated tablets* or its active substance benfotiamine have been identified, and there were no marketing authorisation withdrawals or suspensions for safety reasons, failures to obtain a marketing authorisation renewal, formulation changes restrictions on distribution, risk management activities for safety reasons or actions taken due to product defects and quality issues.

Risk management activities, including

- significant restrictions on distribution or introduction of other risk minimisation measures;
- communications to health care professionals
- significant safety-related changes in labelling documents including restrictions on use or population treated;
- new post-marketing study requirement(s) imposed by competent authorities

were not required for *milgamma protekt film-coated tablets* during the report period.

No new data with a possible impact on the conduct of (specific) clinical trials or the overall clinical development programme have been identified during the report period. There were no refusals to authorise a clinical trial for ethical or safety reasons, partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy, or recall of the investigational drug or comparator.

Risk management activities, including

- protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in
- study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
- restrictions in study population or indications;
- changes to the informed consent document relating to safety concerns; formulation changes;
- addition by regulators of a special safety-related reporting requirement;

- issuance of a communication to investigators or healthcare professionals; and
- plans for new studies to address safety concerns

were not necessary during the report period.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The Summary of Product Characteristics (SmPC) of *milgamma protekt film-coated tablets* of Wörwag Pharma GmbH & Co KG in effect at the end of the period covered by this report represents the Company Core Data Sheets (CCDS) including the company Core Safety Information (CCSI) for *milgamma protekt film-coated tablets* of Wörwag Pharma GmbH & Co KG.

Any recommendations or assessments given in this DSUR refer to the information given in the SmPC of *milgamma protekt film-coated tablets* (See Appendix 1).

There were no safety relevant changes to the reference product information in the report period. The current reference information of *milgamma protekt film-coated tablets* is attached.

5. INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD

This DSUR only relates to a single study (WOE_2013_SB).

Sponsor's protocol code number	**WOE_2013_SB**
Phase	III
Status	Prematurely ended
Countries	Germany (Diabetes Schwerpunktpraxis Essen)
Study title (abbreviated)	***EFFECTS OF BENFOTIAMINE ON INTRAEPIDERMAL NERVE FIBER DENSITY (IENFD) AND DIABETIC NEUROPATHY IN SUBJECTS WITH SENSORIMOTOR DIABETIC POLYNEUROPATHY: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP PILOT STUDY OVER 12 MONTHS.***
Study design	Mono-centric, randomized, placebo-controlled, double blind, parallel group pilot study
Dosing regimen	Group 1 will receive benfotiamine 600 mg/day for 3 months followed by

	benfotiamine 300 mg/day for the rest of the study duration. Group 2 will receive a similar dose of placebo.
Study population	Patients with T1DM or T2DM and DSP
Date of clinical trial start (marked by date of activation of first site)	09.09 2013
Planned enrolment	The study planned to enroll 22 patients who received placebo and active ingredient tablets.
Estimates of cumulative numbers of exposed subjects (based upon total number of patients recruited)	11 patients will be evaluated from 22 planned patients.

6. ESTIMATED CUMULATIVE EXPOSURE

6.1. CUMULATIVE SUBJECT EXPOSURE IN THE DEVELOPMENT PROGRAMME

22 patients could be evaluated for this study.
The patients were 45 to 77 years old; the median age was 63.5 years.
6 patients had type I diabetes, and 16 patients had type II diabetes. The duration of diabetes varied from 4 to 50 years, the median duration was 16 years. 18 of the 22 patients were insulin dependent. 13 patients were treated with oral antidiabetics.
Height and weight of the patients was measured to calculate the Body-Mass-Index (BMI). The BMI varied from 26.6 to 43.9. The median value was 34.6.
The ethnicity is not available for the study as it is not being collected as part of the trial data.

A cumulative summary tabulation by age and sex is provided in Appendix 4.

6.2. PATIENT EXPOSURE FROM MARKETING EXPERIENCE

For the application of benfotiamine no DDD is named till now. Unless otherwise prescribed the usual dosage is 1 film coated tablet (300 mg benfotiamine) once a day. Therefore the estimated number of daily doses (patient treatment days) from a period of 08/03/2012 to 08/02/2016 was 75,381,360 (corresponding to 478,621,200 mg benfotiamine).

There is no temporal limitation of the application. One can assume that the medical treatment is carried out through a period of 3 months on average. The number of daily doses divided by the number of average medical treatment days (approximately 90) leads to 8375 571 patients treated with *milgamma protekt film-coated tablets* from 08/03/2012 to 08/02/2016. This

calculation assumes that patients received 1 coated tablet daily and used the medication continuously over the time of three months.

7. DATA IN LINE LISTINGS AND SUMMARY TABULATIONS

7.1. REFERENCE INFORMATION

The German SmPC of *milgamma protekt film-coated tablets* (last updated May 2014) was used as Reference Safety Information for determining expectedness.

7.2. LINE LISTINGS OF SERIOUS ADVERSE REACTIONS DURING THE REPORTING PERIOD

No serious adverse reactions occurred during the reporting period (02 Dec 2014 to 22 Oct 2015).

7.3. CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS

	Total up to 22-Oct-2015	
	Study drug	Placebo
ADRs by SOC and PT		
Cardiac disorders		
Angina pectoris	1	0
Subtotal	*1*	*0*
General disorders and administration site conditions		
Sudden cardiac death	1	0
Subtotal	*1*	*0*
Injury, poisoning and procedural complications		
In-stent coronary artery restenosis	1	0
Subtotal	*1*	*0*
Nervous system disorders		
Cerebrovascular accident	0	1
Subtotal	*0*	*1*
Respiratory, thoracic and mediastinal disorders		
Cough	1	0
Dyspnoea	2	0
Subtotal	*3*	*0*
TOTAL	***6***	***1***

8. SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

8.1. COMPLETED CLINICAL TRIALS

During the reporting period, Wörwag Pharma analysed data only from the single study (WOE_2013_SB) investigating benfotiamine, which is covered by this DSUR.

As a pilot study this study is of considerable significance. Unfortunately, different labs couldn't see any nerve fibers on the samples received. Therefore, from ethical point of view; we decided to terminate the study prematurely and don't expose the patients for further skin biopsy. The study delivered some interesting results that are important for the planning of a skin-study.

No serious adverse reactions occurred during the reporting period (02 Dec 2014 to 22 Oct 2015).

There have been 4 AEs in 4 patients during the reporting period:

Random No.	AEs	Intensity	Relation to study medication or study procedures	Action taken	Outcome
111	Vasovagal reaction during biopsy	Moderate	Related to study procedure	Postural treatment	Recovered
113	Elective coronary angiography	Mild	Not related	Implantation of coronary stent	Recovered
114	Arterial Hypertension (newly diagnosed)	Mild	Not related	Antihypertensive medication started	Not Recovered
118	Diabetic foot ulcer Dig III right foot	Mild	Not related	Local treatment	Recovered

The events were either assessed as related to the study procedure or not related to the investigational product.

8.2. ONGOING CLINICAL TRIALS

Not applicable. Woerwag Pharma is not sponsoring another study trialling benfotiamine.

8.3. LONG-TERM FOLLOW-UP

This section is not applicable.

8.4. OTHER THERAPEUTIC USE OF INVESTIGATIONAL DRUG

This section is not applicable as we do not have access or compassionate use programmes.

8.5. NEW SAFETY DATA RELATED TO COMBINATION THERAPIES

This section is not applicable.

9. SAFETY FINDINGS FROM NON-INTERVENTIONAL STUDIES

Woerwag Pharma is sponsoring non-interventional study trialling benfotiamine in Romania.

10. OTHER CLINICAL TRIAL/STUDY SAFETY INFORMATION

Not applicable. No other relevant safety information from other clinical trials/studies investigating benfotiamine has become available to Woerwag Pharma during the reporting period.

11. SAFETY FINDINGS FROM MARKETING EXPERIENCE

Treatment with *milgamma protekt film-coated tablets* is predominantly well-tolerated in the recommended doses. Possible adverse reactions and interactions are listed in the SmPC and PIL of *milgamma protekt film-coated tablets.*

No further important safety concerns were identified during the reporting period related to *milgamma protekt film-coated tablets.*

Critical gaps in the knowledge regarding the safety of the product *milgamma protekt film-coated tablets* have not been identified,

12. NON-CLINICAL DATA

No new non-clinical data from *in vivo* and *in vitro* studies has become available to Woerwag Pharma during the reporting period.

13. LITERATURE

This section includes a summary of new and significant efficacy and safety findings published in the worldwide literature during the report period, i.e. from 02 Dec 2014 to 22

Oct 2015 which are considered relevant for *milgamma mono 300 film-coated tablets* or benfotiamine.

During the report period no adverse reactions associated with the use of *Benfogamma® 300 mg film-coated tablets*, *milgamma® protekt* or *milgamma® mono 300* were reported in the relevant medical literature.

However, adverse reactions associated with the use of the active ingredient benfotiamine or the use of thiamine were published in the relevant medical literature.

Literature citations referenced to this section can be found in Appendix 7.2.

Overall, the literature of the reporting period supports the generally favourable benefit-risk balance of benfotiamine and there is no indication of hitherto unknown risks.

Pregnancy outcomes (including termination) with no adverse outcomes:

No new and significant findings with regard to use of benfotiamine in pregnancy are available from literature of the period covered.

Use in paediatric populations:

No new and significant findings with regard to use of benfotiamine in children are available from literature of the period covered.

Compassionate use:

No new and significant findings with regard to compassionate use of benfotiamine are available from literature of the period covered.

Lack of efficacy:

No new and significant findings that may indicate any lack of efficacy of benfotiamine are available from literature of the period covered.

Asymptomatic overdose, abuse or misuse:

No new and significant findings with regard to asymptomatic overdose, abuse or misuse in connection with benfotiamine are available from literature of the period covered.

Medication error, where no adverse events occurred:

No new and significant findings with regard to medication errors in connection with benfotiamine are available from literature of the period covered.

Important non-clinical safety results:

No new and significant non-clinical safety results were found in the literature of the report period.

Genotype polymorphismus:

No new and significant findings are available from literature of the period covered,

Altogether, no new and significant findings are available in the literature of the covered period that may lead to changes in the benefit/risk assessment of benfotiamine.

14. OTHER DSURS

This section is not applicable, as there are no other DSURs submitted by Woerwag Pharma for benfotiamine in this reporting period.

15. LACK OF EFFICACY

An unusual level of "lack of efficacy" reporting, which might represent a significant hazard to the patients treated with *milgamma protekt film-coated tablets,* was not identified during the report period.

16. REGION-SPECIFIC INFORMATION

This section is not applicable for this mono-centric study.

17. LATE-BREAKING INFORMATION

There was no significant safety information between the data lock point for this report and the time of submission.

18. OVERALL SAFETY ASSESSMENT

18.1. EVALUATION OF THE RISKS

A small number of possible adverse reactions has been identified following analysis of the reporting period of the respective study with benfotiamine.

There have been 4 AEs in 4 patients during the reporting period (see chapter 8.1)

As of the data at data lock point (22/10/2015), 3 case reports corresponding to 7 SAEs have been reported **cumulatively**. The trial safety profile remains unchanged and is in line with the current information available in the SmPC. There have been no safety issues highlighted to Woerwag Pharma.

Dspnoe:

Dyspnoe and cough are unexpected adverse reactions of benfotiamine. The investigator assessed this SAE as doubtfully related to the benfotiamine.

Cerebrovascular accident:

Unblinding of the case revealed that the patient was receiving placebo. Therefore no changes in the product information to *milgamma protekt film-coated tablets* are required.

Sudden cardiac death (additional reactions: angina pectoris, coronary artery stenosis, dyspnoea):

In-stent coronary artery restenosis, dyspnoea, angina pectoris and sudden cardiac death are unexpected adverse reactions of benfotiamine. The investigator assessed this SAE as possibly related to the benfotiamine. The Sponsors QPPV's opinion is that the event is not related to the investigational product.
The concerned 68-year-old woman was a multimorbid and polymedicated patient.
Her medical history and concomitant treatment indicate that the events might have happened with or without IMP. Therefore no changes in the product information to *milgamma protekt film-coated tablets* are required.

Based on the presented data, there are no newly identified risks for benfotiamine or the product *milgamma protekt film-coated tablets.*

Evaluation of the available data has not revealed any gaps in the knowledge about the product.

From the MAHs own data, no newer information about the following drug risks has been available in the report period:

- toxicity not observed up to now
- serious unlisted reactions
- increased incidence of hitherto listed reactions
- drug abuse
- risks with respect to special patient groups
- drug interactions
- experience with overdose, deliberate or accidental, and its treatment
- positive or negative experiences during pregnancy or lactation
- experience in special patient groups
- effects of long-term treatment.

18.2. BENEFIT-RISK CONSIDERATIONS

Benfotiamine is a well-established substance.

The primary study parameter planned to measure the changes from baseline in intra-epidermal nerve fiber density (IENFD) after 6 and 12 months of benfotiamine treatment compared to placebo. The samples measured by different labs and they couldn't see any nerve fibers on the samples received to the labs. Therefore, from ethical point of view; we decided to terminate the study prematurely and don't expose the patients for further skin biopsy.

Overall, in the period under review there were no reports identified in this study that gave reason for a change in the assessment of the benefit-risk profile of benfotiamine and *milgamma protekt film-coated tablets*.

No new information relevant to the safety of benfotiamine and *milgamma protekt film-coated tablets* has become available from this study during the report period, which covers the period from 02.12.2014 to 22.10.2015.

Accordingly, benfotiamine and *milgamma protekt film-coated tablets* continue to have a positive benefit-risk profile.

19. SUMMARY OF IMPORTANT RISKS

This section summarises the important identified and potential risks that have been identified for *milgamma protekt film-coated tablets*.

No risks have not been newly identified within the study described in this DSUR. The listed risks are already described in the SmPC and PIL of *milgamma protekt film-coated tablets*.

Summary of safety concerns	
Important identified risks	• Hypersensitivity to benfotiamine/ thiamine or one of the other ingredients of the medicinal product. • Thiamine is deactivated by 5-fluorouracil since 5-fluorouracil competitively inhibits the phosphorylation of thiamine to thiamine pyrophosphate.
Important potential risks	• Gastrointestinal disorders like nausea and other gastrointestinal complaints

No additional risk minimisation activities are considered necessary at the moment.

20. CONCLUSIONS

This DSUR for benfotiamine has been prepared under the authority of Wörwag Pharma GmbH & Co KG.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, no changes to the reference safety information or new risk minimisation activities are deemed necessary at this time.

Accordingly, benfotiamine and *milgamma protekt film-coated tablets* continue to be considered a safe and effective medicinal product with a positive benefit-risk ratio.

21. APPENDICES TO THE DSUR

Documents	✓/Not applicable
1. Investigator Brochure or SmPC (include version and date)	✓
2. Cumulative Table of important regulatory advice	Not applicable
3. Status of ongoing and completed clinical trials	✓
4. Cumulative Summary Tabulations of Demographic Data	✓
5. Line listing of serious adverse reactions (SARs)	Not applicable
6. Cumulative summary tabulations of serious adverse events (SAEs)	✓
7. Scientific abstracts / References	✓

APPENDIX 1

Fachinformation

1. BEZEICHNUNG DES ARZNEIMITTELS

mil*gamma*® protekt
Wirkstoff: Benfotiamin 300 mg
Filmtabletten

2. QUALITATIVE UND QUANTITATIVE ZUSAMMENSETZUNG

1 Filmtablette enthält 300 mg Benfotiamin (lipidlösliches Vitamin-B_1-Derivat).

Die vollständige Auflistung der sonstigen Bestandteile siehe Abschnitt 6.1.

3. DARREICHUNGSFORM

Weiße, längliche Filmtablette mit Bruchkerbe.
Die Tablette kann in gleiche Dosen geteilt werden.

4. KLINISCHE ANGABEN

4.1 Anwendungsgebiete

Gesicherte Anwendungsgebiete für die Monopräparate sind ausschließlich Therapie oder Prophylaxe von klinischen Vitamin-B1-Mangelzuständen, sofern diese nicht ernährungsmäßig behoben werden können.

Der klinisch gesicherte Vitamin-B1-Mangel kann auftreten bei:
Mangel- und Fehlernährung (z.B. Beriberi), parenteraler Ernährung über lange Zeit, Null-Diät, Hämodialyse, Malabsorption, chronischem Alkoholismus (alkoholtoxische Kardiomyopathie, Wernicke-Enzephalopathie, Korsakow-Syndrom), gesteigertem Bedarf (z.B. Schwangerschaft und Laktation).

Behandlung von Neuropathien und kardiovaskulären Störungen, die durch Vitamin-B1-Mangel hervorgerufen werden.

4.2 Dosierung und Art der Anwendung

Soweit nicht anders verordnet, 1 x täglich 1 Filmtablette einnehmen.

Die Filmtabletten werden unzerkaut mit etwas Flüssigkeit eingenommen.

Die Dauer der Einnahme richtet sich nach dem therapeutischen Erfolg.

Zur Therapie von Neuropathien sollte mil*gamma*® protekt initial über einen Zeitraum von mindestens 3 Wochen eingenommen werden. Anschließend Weiterbehandlung gemäß therapeutischem Erfolg. Sollte nach vier Wochen keine oder eine zu geringe Wirkung erkennbar sein, sollte die Therapie der Beschwerden überprüft werden.

4.3 Gegenanzeigen

- Überempfindlichkeit gegenüber Benfotiamin/Thiamin oder einem der sonstigen Bestandteile von mil*gamma*® protekt

4.4 Besondere Warnhinweise und Vorsichtsmaßnahmen für die Anwendung

Keine.

4.5 Wechselwirkungen mit anderen Arzneimitteln und sonstige Wechselwirkungen

Thiamin wird durch 5-Fluoruracil inaktiviert, da 5-Fluoruracil kompetitiv die Phosphorylierung von Thiamin zu Thiaminpyrophosphat hemmt.

4.6 Fertilität, Schwangerschaft und Stillzeit

In der Schwangerschaft und Stillzeit beträgt die empfohlene tägliche Zufuhr für Vitamin B1 1.4-1.6 mg. In der Schwangerschaft darf diese Dosierung nur überschritten werden, wenn bei der Patientin ein nachgewiesener Vitamin-B1-Mangel besteht, da die Sicherheit einer Anwendung höherer als der täglich empfohlenen Dosis bislang nicht belegt ist. Vitamin B1 geht in die Muttermilch über.

4.7 Auswirkungen auf die Verkehrstüchtigkeit und die Fähigkeit zum Bedienen von Maschinen

Es sind keine besonderen Vorsichtsmaßnahmen erforderlich.

4.8 Nebenwirkungen

Bei der Bewertung von Nebenwirkungen werden folgende Häufigkeitsangaben zugrundegelegt:

Sehr häufig: ≥ 10 %
Häufig: ≥ 1% - < 10%
Gelegentlich: ≥ 0,1 % - < 1%
Selten: ≥ 0,01 % - < 0,1%
Sehr selten: < 0,01%, einschließlich Einzelfälle

In Einzelfällen kann es zu Überempfindlichkeitsreaktionen kommen (Urtikaria, Exanthem).
In klinischen Studien wurden Einzelfälle von gastrointestinalen Störungen wie z. B. Übelkeit oder andere Beschwerden dokumentiert. Ein kausaler Zusammenhang mit Vitamin B1 sowie eine mögliche Dosisabhängigkeit sind noch nicht ausreichend geklärt.

Meldung des Verdachts auf Nebenwirkungen

Die Meldung des Verdachts auf Nebenwirkungen nach der Zulassung ist von großer Wichtigkeit. Sie ermöglicht eine kontinuierliche Überwachung des Nutzen-Risiko-Verhältnisses des Arzneimittels. Angehörige von Gesundheitsberufen sind aufgefordert, jeden Verdachtsfall einer Nebenwirkung dem

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger Allee 3
D-53175 Bonn
Website: http://www.bfarm.de

anzuzeigen.

4.9 Überdosierung

Bei der vorliegenden oralen Anwendung ist infolge der großen therapeutischen Breite bisher keine Überdosierung bekannt geworden.

5. PHARMAKOLOGISCHE EIGENSCHAFTEN

5.1 Pharmakodynamische Eigenschaften

Pharmakotherapeutische Gruppe: Vitamine

ATC-Code: A11DA03

Vitamin B_1 ist ein essentieller Wirkstoff. Das lipidlösliche Pro-Drug Benfotiamin wird im Organismus zu biologisch wirksamem Thiaminpyrophosphat (TPP) umgewandelt. TPP greift in

wichtige Funktionen des Kohlenhydratstoffwechsels ein. Thiaminpyrophosphat wirkt als Coenzym bei der Umwandlung von Pyruvat zu Acetyl-COA und bei der Transketolase im Pentosephosphatzyklus. Außerdem wirkt es bei der Umwandlung von Alpha-Ketoglutarat zu Succinyl-COA im Zitronensäurezyklus. Aufgrund enger Verknüpfungen im Stoffwechsel bestehen Wechselwirkungen mit den übrigen Vitaminen des B-Komplexes.

Die Cocarboxylase ist u.a. Coenzym der Pyruvatdehydrogenase , die eine Schlüsselstellung im oxidativen Glukoseabbau einnimmt. Da die Energiegewinnung in den Nervenzellen hauptsächlich durch oxidativen Glukoseabbau erfolgt, ist die ausreichende Versorgung mit Thiamin für die Funktion der Nerven unerlässlich. Bei erhöhten Glukosespiegeln ist ein Mehrbedarf an Thiamin vorhanden.

Das Fehlen ausreichender Cocarboxylasemengen im Blut führt zu einer Anreicherung intermediärer Abbauprodukte wie Pyruvat, Lactat und Ketoglutarat in Blut und Geweben, auf die die Muskulatur, das Myokard und das ZNS besonders empfindlich reagieren. Benfotiamin hemmt die Kumulation dieser toxischen Stoffe.

Zur Bestimmung des Vitamin-B_1-Status sind Messungen von thiamindiphosphatabhängigen Enzymaktivitäten in den Erythrozyten, wie z.B. Transketolase (ETK) und das Ausmaß ihrer Aktivierbarkeit (Aktivierungskoeffizient α-ETK) geeignet. Die Konzentrationen für ETK im Plasma liegen zwischen 2 und 4 µg/100 ml.

Eine antineuralgische Wirkung von Vitamin B_1 (bzw. Benfotiamin) wurde in tierexperimentellen Modellen nachgewiesen. Aus der Behandlung von Alkoholikern ist ein positiver Einfluss auf Transketolasen als Aktivierungsfaktoren bekannt.

Die Wirksamkeit hochdosierter Gaben von Vitamin B_1 in der Therapie der Wernicke-Enzephalopathie ist erwiesen und wird als Hinweis auf eine direkte ZNS-Wirkung des Vitamins gewertet.

Die Wirksamkeit von Benfotiamin bei der diabetischen Polyneuropathie ist in mehreren doppelblinden placebokontrollierten Studien belegt. In der Studie von Ledermann (1989) wurde ein Kombinationspräparat aus Benfotiamin, Vitamin B6 und Vitamin B12 eingesetzt. Im Therapieverlauf kam es bereits innerhalb von 3 Wochen zu einer signifikanten Verbesserung von Neuropathiescore und Vibrationsempfinden. Innerhalb des Scores kam es zu einer signifikanten Besserung der Sensibilitätsstörungen. Bei den Schmerzsensationen wurde unter Verum bei 47% der Patienten eine Besserung erzielt, unter Placebo nur bei 10% der Patienten.

Die Untersuchung von Stracke und Federlin (1996) belegt die Wirksamkeit eines Benfotiamin-haltigen Kombinationspräparates bei diabetischer Polyneuropathie anhand des objektiven Parameters der Nervenleitgeschwindigkeit. Auch die Langzeitbeobachtung, die über insgesamt 12 Monate durchgeführt wurde, bestätigte diesen positiven Effekt.

In einer weiteren placebokontrollierte Doppelblind-Studie wurde mit einem Benfotiamin-Monopräparat eine signifikante Besserung des Neuropathiescores erzielt (firmeninterne Daten, 1993).

5.2 Pharmakokinetische Eigenschaften

Vitamin B_1 liegt in den meisten Nahrungsmitteln in der biologisch aktiven Form als Thiaminpyrophosphat vor. Zur Resorption muss der Phosphatrest an der Darmwand durch die dort

vorhandenen Pyrophosphatasen abgespalten werden. Für die Resorption von Thiamin wird ein dosisabhängiger dualer Transportmechanismus angenommen, und zwar eine aktive Resorption bei einer applizierten Menge bis zu 2 µmol und eine passive Diffusion bei höheren Dosen.
Ca. 1 mg Thiamin wird täglich im Organismus abgebaut. Ein Überschuss an Thiamin wird über den Urin ausgeschieden.
Nach oraler Gabe des lipidlöslichen Pro-Drug Benfotiamin erfolgt im Darm durch Phosphatasen eine Dephosphorylierung in das fettlösliche S-Benzoylthiamin (SBT). Dieses wird besser resorbiert als die wasserlöslichen Thiaminderivate und gelangt aus dem zirkulierenden Blut ins Zellinnere. Dort erfolgt die enzymatische Debenzoylierung zu Thiamin, das anschließend durch Thiaminkinase in die aktive Coenzymform (Cocarboxylase, syn. Thiamindiphosphat) umgewandelt wird. Mit Benfotiamin werden intrazellulär wesentlich höhere Konzentrationen an Thiamin und den aktiven Coenzymen erzielt als mit oral verabreichten wasserlöslichen Thiaminderivaten.
Die Resorption von Benfotiamin erfolgt dosisproportional, da die Substanz aufgrund ihrer Fettlöslichkeit im Gegensatz zu Thiamin keiner Sättigungskinetik unterliegt.

Von Benfotiamin konnte nachgewiesen werden, dass im Organismus die biologisch aktiven Coenzyme Thiaminpyrophosphat und -triphosphat entstehen. Anhand von Ganztierautoradiographien konnten mit markiertem Benfotiamin besonders hohe Radioaktivitäten im Gehirn, Herzmuskel und Zwerchfell nachgewiesen werden.

5.3 Präklinische Daten zur Sicherheit

a) Akute, subchronische und chronische Toxizität
Beim Tier bewirken sehr hohe Dosen von Vitamin B1 Bradykardien. Daneben treten Symptome einer Blockade der vegetativen Ganglien und Muskelendplatten auf.

Im Tierversuch zur chronischen Toxizität wurden bei Dosen von 100 mg/kg Benfotiamin keine organpathologischen Veränderungen festgestellt.

b) Mutagenes und tumorerzeugendes Potential
Unter den Bedingungen der klinischen Anwendung sind mutagene Wirkungen von Vitamin B1 nicht zu erwarten.

Langzeitstudien am Tier zum tumorerzeugenden Potential von Vitamin B1 liegen nicht vor.

c) Reproduktionstoxizität
Vitamin B1 wird aktiv in den Fetus transportiert. Die Konzentrationen in Feten und Neugeborenen liegen über den maternalen Vitamin-B1-Konzentrationen.

Hohe Dosen von Vitamin B1 wurden im Tierversuch unzureichend untersucht.

6. PHARMAZEUTISCHE ANGABEN

6.1 Liste der sonstigen Bestandteile

Mikrokristalline Cellulose, Talkum, Povidon (K30), hochdisperses Siliciumdioxid, Croscarmellose-Natrium, höherkettige Partialglyceride, Hypromellose, Titandioxid, Polyethylenglycol, Saccharin – Natrium

6.2 Inkompatibilitäten

Bisher keine bekannt.

6.3 Dauer der Haltbarkeit

5 Jahre

6.4 Besondere Vorsichtsmaßnahmen für die Aufbewahrung

keine

6.5 Art und Inhalt des Behältnisses

Originalpackung mit 30, 60, 90 und 100 Filmtabletten.
Klinikpackungen mit 500, 1.000 und 5.000 Filmtabletten.
Es werden möglicherweise nicht alle Packungsgrößen in den Verkehr gebracht.

6.6 Besondere Vorsichtsmaßnahmen für die Beseitigung

Das Arzneimittel darf nicht im Abwasser oder Haushaltsabfall entsorgt werden. Diese Maßnahme hilft die Umwelt zu schützen.

7. INHABER DER ZULASSUNG

Wörwag Pharma GmbH & Co. KG
Calwer Str. 7
71034 Böblingen
Tel.: 07031/ 6204-0
Fax: 07031/ 6204-31
e-mail: info@woerwagpharma.com

8. ZULASSUNGSNUMMER

6366586.00.00

9. DATUM DER ERTEILUNG DER ZULASSUNG

23.06.2005

10. STAND DER INFORMATION

05/2014

11. VERKAUFSABGRENZUNG

Apothekenpflichtig

---

weitere Angaben:

Das lipidlösliche Pro-Drug Benfotiamin unterscheidet sich in seinen kinetischen Eigenschaften wesentlich von wasserlöslichen Thiaminderivaten. Die vielfach höhere Bioverfügbarkeit von Benfotiamin ist im Vergleich zu Thiaminmononitrat (Bitsch, 1990) belegt. Auch unter körperlicher Belastung werden mit Benfotiamin signifikant höhere Thiaminspiegel im Plasma, Hämolysat und in den Erythrozyten erzielt als mit wasserlöslichen Thiaminderivaten, wie eine Bioverfügbarkeitsuntersuchung an 20 Sportlern gezeigt hat (Beuker, 1996). Für Benfotiamin wurde nach Gabe einer äquimolaren Menge eine etwa 5fach höhere Bioverfügbarkeit im Vergleich zu Thiaminmononitrat ermittelt. Die maximale Plasmakonzentration (c_{max}) war bis zu 16fach höher (firmeninterne Daten, 1996).

APPENDIX 2 - CUMULATIVE TABLE OF IMPORTANT REGULATORY ADVICE

Not applicable

APPENDIX 3 - STATUS OF ONGOING AND COMPLETED CLINICAL TRIALS

This DSUR only relates to a single study (WOE_2013_SB).

Sponsor's protocol code number	**WOE_2013_SB**
Phase	III
Status	Prematurely ended
Countries	Germany (Diabetes Schwerpunktpraxis Essen)
Study title (abbreviated)	***EFFECTS OF BENFOTIAMINE ON INTRAEPIDERMAL NERVE FIBER DENSITY (IENFD) AND DIABETIC NEUROPATHY IN SUBJECTS WITH SENSORIMOTOR DIABETIC POLYNEUROPATHY: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP PILOT STUDY OVER 12 MONTHS.***
Study design	Mono-centric, randomized, placebo-controlled, double blind, parallel group pilot study
Dosing regimen	Group 1 will receive benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for the rest of the study duration. Group 2 will receive a similar dose of placebo.
Study population	Patients with T1DM or T2DM and DSP
Date of clinical trial start (marked by date of activation of first site)	09.09 2013
Planned enrolment	The study planned to enroll 22 patients who received placebo and active ingredient tablets.
Estimates of cumulative numbers of exposed subjects (based upon total number of patients recruited)	11 patients will be evaluated from 22 planned patients.

APPENDIX 4 – CUMULATIVE SUMMARY TABULATIONS OF DEMOGRAPHIC DATA

Patient ID. No.	Gender	Date of Birth	Age
001	M	1953	**62**
002	M	1940	75
003	W	1948	67
004	M	1950	65
005	W	1946	**69**
006	M	1968	**47**
007	W	1936	78
008	M	1945	**70**
009	W	1962	**53**
010	M	1957	**58**
011	M	1947	**68**
012	W	1943	**72**
013	W	1945	**70**
014	M	1946	**69**
015	W	1949	**66**
016	M	1948	67

Total treated patients = 11

Total after drop-out patients = 9 patients

APPENDIX 5 - LINE LISTINGS OF SERIOUS ADVERSE REACTIONS (SARS)

Not applicable since there were no SARs during the reporting period.

APPENDIX 6 - SERIOUS ADVERSE EVENTS CUMULATIVE SUMMARY

	Total up to 22-Oct-2015	
	Study drug	Placebo
ADRs by SOC and PT		
Cardiac disorders		
Angina pectoris	1	0
Subtotal	*1*	*0*
General disorders and administration site conditions		
Sudden cardiac death	1	0
Subtotal	*1*	*0*
Injury, poisoning and procedural complications		
In-stent coronary artery restenosis	1	0
Subtotal	*1*	*0*
Nervous system disorders		
Cerebrovascular accident	0	1
Subtotal	*0*	*1*
Respiratory, thoracic and mediastinal disorders		
Cough	1	0
Dyspnoea	2	0
Subtotal	*3*	*0*
TOTAL	***6***	***1***

APPENDIX 7 – SCIENTIFIC ABTRACTS / REFERENCES

7.1: Section 1 - Introduction

[1]	Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG: Benfotiamine in Diabetic Polyneuropathy (BENDIP): Results of a Randomised, Double Blind, Placebo-controlled Clinical Study. *Exp Clin Endocrinol Diabetes* 116:600-605, 2008
[2]	Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M: Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. *Nat Med* 9:294-299, 2003
[3]	Berrone E, Beltramo E, Solimine C, Ape AU, Porta M: Regulation of intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular cells cultured in high glucose. *J Biol Chem* 281(14):9307-9313, 2006
[4]	Schmid U, Stopper H, Heidland A, Schupp N: Benfotiamine exhibits direct antioxidative capacity and prevents induction of DNA damage in vitro. *Diabetes Metab Res Rev* 24:371-377, 2008
[5]	Stracke H, Hammes HP, Werkmann D, Mavrakis K, Bitsch I, Netzel M, Geyer J, Kopcke W, Sauerland C, Bretzel RG, Federlin KF: Efficacy of benfotiamine versus thiamine on function and glycation products of peripheral nerves in diabetic rats. *Exp Clin Endocrinol Diabetes* 109:330-336, 2001
[6]	Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Gotting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschoepe D: Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. *Diabetes Care* 29:2064-2071, 2006
[7]	Stirban A, Nandrean S, Kirana S, Gotting C, Veresiu IA, Tschoepe D: Benfotiamine counteracts smoking-induced vascular dysfunction in healthy smokers. *Int J Vasc Med* 2012:968761, 2012
[8]	Stracke H, Lindemann A, Federlin K: A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. *Exp Clin Endocrinol Diabetes* 104:311-316, 1996
[9]	Haupt E, Ledermann H, Kopcke W: Benfotiamine in the treatment of diabetic polyneuropathy--a three-week randomized, controlled pilot study (BEDIP study). *Int J Clin Pharmacol Ther* 43:71-77, 2005
[10]	Winkler G, Pal B, Nagybeganyi E, Ory I, Porochnavec M, Kempler P: Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy. *Arzneimittelforschung* 49:220-224, 1999
[11]	Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, Hanssen KF: The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month,

	double-blind, randomized, placebo-controlled trial. *Diabetes Care* 35:1095-1097, 2012
[12]	Ziegler D, Tesfaye S, Kempler P: Comment on: Fraser et al. The Effects of Long-Term Oral Benfotiamine Supplementation on Peripheral Nerve Function and Inflammatory Markers in Patients With Type 1 Diabetes: A 24-Month, Double-Blind, Randomized, Placebo-Controlled Trial. Diabetes Care 2012;35:1095-1097. *Diabetes Care* 35:e79, 2012
[13]	Thornalley PJ, Babaei-Jadidi R, Al AH, Rabbani N, Antonysunil A, Larkin J, Ahmed A, Rayman G, Bodmer CW: High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* 50:2164-2170, 2007
[14]	Rieck J, Halkin H, Almog S, Seligman H, Lubetsky A, Olchovsky D, Ezra D: Urinary loss of thiamine is increased by low doses of furosemide in healthy volunteers. *J Lab Clin Med* 134:238-243, 1999
[15]	Sica DA: Loop diuretic therapy, thiamine balance, and heart failure. *Congest Heart Fail* 13:244-247, 2007
[16]	Beiswenger KK, Calcutt NA, Mizisin AP: Epidermal nerve fiber quantification in the assessment of diabetic neuropathy. *Acta Histochem* 110:351-362, 2008
[17]	Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, Hamwi J, Pollari D, Bixby B, Howard J, Singleton JR: Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care* 29:1294-1299, 2006
[18]	Meerwaldt R, Graaff R, Oomen PH, Links TP, Jager JJ, Alderson NL, Thorpe SR, Baynes JW, Gans RO, Smit AJ: Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia* 47:1324-1330, 2004

7.2: Section 13 - Literature

Abdollahifard S, Rahmanian Koshkaki A, Moazamiyanfar R. The effects of vitamin B1 on ameliorating the premenstrual syndrome symptoms. Glob J Health Sci. 2014 Jul 29;6(6):144-53. doi: 10.5539/gjhs.v6n6p144. /2014-07-29/
Dai Z, Koh WP, B-Vitamins and Bone Health-A Review of the Current Evidence, Nutrients, 2015 May 7;7(5):3322-3346, /2015-05-07/
Kosaka T, et al, The etiology of cortical lesions in Marchiafava-Bignami disease is nicotinic acid deficiency: A case report and review of the literature, Neurology 84 (Suppl, P026): No, 14, 6 Apr 2015, Available from: URL: http://www.neurology.org/content/84/14_Supplement/P6.024.short [abstract] - Japan
Mine S, et al, Evidence for human herpesvirus-6B infection of regulatory T-cells in acute systemic lymphadenitis in an immunocompetent adult with the drug reaction with eosinophilia and systemic symptoms syndrome: A case report, Journal of Clinical Virology 61: 448-452, No, 3, Nov 2014, Available from: URL: http://doi.org/10.1016/j.jcv.2014.08.025 - Japan

Raval AD; Thakker D; Rangoonwala AN; Gor D; Walia R. Vitamin B and its derivatives for diabetic kidney disease. Cochrane Database of Systematic Reviews (2015 Issue 1); p. CD009403 /2015 1. Issue/ DOI: 10.1002/14651858.CD009403.pub2 /2015-01-01/
Swaminathan S, Thomas T, Kurpad AV, B-vitamin interventions for women and children in low-income populations, Curr Opin Clin Nutr Metab Care, 2015 Mar 24, /2015-03-24/
Xie F, Cheng Z, Li S, Liu X, Guo X, Yu P, Gu Z, Pharmacokinetic study of benfotiamine and the bioavailability assessment compared to thiamine hydrochloride, J Clin Pharmacol, 2014 Jun;54(6):688-95, doi: 10,1002/jcph,261, /2014-06-01/ China