swissmedic

Date: 11 May 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

milgamma

International non-proprietary name: benfotiamine
Pharmaceutical form: film-coated tablets
Dosage strength(s): 300 mg
Route(s) of administration: oral
Marketing authorisation holder: Maras AG
Marketing authorisation no.: 68695
Decision and decision date: approved on 6 April 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for benfotiamine in the above-mentioned medicinal product.

Authorisation in accordance with Article 14 para. 1 a$^{bis\text{-}quater}$ TPA
The applicant requested a simplified authorisation procedure in accordance with Article 14 para. 1 a$^{bis\text{-}quater}$ TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of conditions that are responsive to vitamin B1 administration, such as treatment and prophylaxis of vitamin B1 deficiency conditions, if they cannot be solved by dietary means.
Treatment of neurological disorders associated with vitamin B1 deficiency, such as alcoholic or diabetic polyneuropathy, which can manifest in sensory impairments (e.g. pain, tingling, numbness) in the extremities.
Treatment of cardiovascular disorders associated with vitamin B1 deficiency in diabetic patients.

2.2.2 Approved indication

Treatment of disorders responding to administration of vitamin B1, such as:
- treatment and prophylaxis of vitamin B1 deficiency that cannot be corrected by dietary means;
- treatment of neurological disorders associated with vitamin B1 deficiency, such as alcoholic or diabetic polyneuropathy, which can manifest as sensory disturbances (e.g. pain, tingling, numbness) in the extremities;
- treatment of cardiovascular disease associated with vitamin B1 deficiency in people with diabetes mellitus.

milgamma is used in adults.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Adults from 18 years:

Prophylaxis of vitamin B1 deficiency conditions:
½ - 1 film-coated tablet daily.

Treatment of vitamin B1 deficiency:
1 film-coated tablet daily

Treatment of neurological and cardiovascular disorders associated with vitamin B1 deficiency:
1-2 film-coated tablet(s) daily for at least 3 weeks, followed by ½ - 1 tablet daily.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	4 October 2021
Formal control completed	2 November 2021
List of Questions (LoQ)	14 June 2022
Response to LoQ	28 September 2022
Preliminary decision	9 December 2022
Response to preliminary decision	23 January 2023
Final decision	4 April 2023
Decision	approval

For the application for the authorisation of the medicinal product milgamma, Swissmedic has reviewed the quality exclusively on the basis of primary data. The authorisation of milgamma is based primarily on the medicinal product milgamma mono 300, which contains the same active substance and has been authorised in Germany for more than 10 years. Apart from the quality-related aspects for which Swissmedic has conducted an independent scientific review, this SwissPAR refers to the authorisation of the foreign medicinal product milgamma mono 300.

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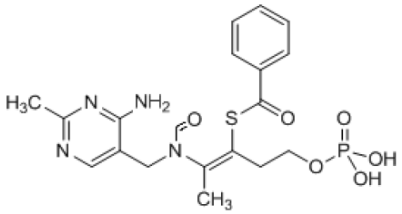
3 Quality aspects

3.1 Drug substance

INN:	Benfotiamine
Chemical name:	S-[(Z)-2-[(4-amino-2-methylpyrimidin-5-yl)methyl-formylamino]-5-phosphonooxypent-2-en-3-yl] benzenecarbothioate
Molecular formula:	$C_{19}H_{23}N_4O_6PS$
Molecular mass:	466.45 g/mol

Molecular structure:



Physicochemical properties:
White crystals or crystalline powder, slightly hygroscopic, slightly soluble in water. A saturated solution of benfotiamine is acidic. Benfotiamine exists in different crystalline forms.

Synthesis:
The preparation of the drug substance is carried out by different manufacturers. The manufacturing processes have been adequately described and the processes are controlled with appropriate in-process controls and tests for isolated intermediates, where applicable.

Specification:
In order to ensure a consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The correct polymorphic form is controlled by infrared spectroscopy. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:
Appropriate stability data have been presented. Based on the results, satisfactory re-test periods have been established when stored in an air-tight container, protected from light.

3.2 Drug product

Description and composition:
milgamma drug product is a white oblong film-coated tablet with breaking notch on both sides, containing 300 mg of benfotiamine. The excipients used in the drug product are widely used in pharmaceutical preparations for oral solid dosage forms and meet the standards defined in the common compendial monographs. Divisibility for dosing purposes was shown in accordance to Ph.Eur.

Pharmaceutical development:
The oral application of benfotiamine is a suitable route of administration, as benfotiamine does not decompose in the conditions in the gastrointestinal tract, and it is easily absorbed in the small intestine. The tablets are coated to cover the bitter taste of the drug substance.

Manufacture:
The manufacturing process used is a standard process for the manufacture of solid oral dosage forms. The manufacturing principle is based on the method of direct compression of the cores, followed by coating.

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Specification:
Adequate tests and acceptance criteria for release and shelf-life have been established for the control of the finished product. The specifications include relevant physicochemical characteristics, identification of the drug substance as well as assay and purity tests.

Container closure system:
The container closure system for the drug product is a blister with a PVC/PVDC film and an aluminium foil backing. The materials comply with the current European guidelines and recommendations and the Ph. Eur. specifications.

Stability:
Appropriate stability data have been generated according to the relevant international guidelines. The storage recommendations are “Do not store above 30°C”, and to keep the blister in its original packaging to protect the content from light.

3.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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4 Nonclinical aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has only reviewed the nonclinical overview for the authorisation of milgamma. The approval of milgamma is based on the medicinal product milgamma mono 300, which contains the same active substance and has been authorised in Germany for more than 10 years.

5 Clinical and clinical pharmacology aspects

For the application for the authorisation of the medicinal product milgamma, Swissmedic has conducted only a summary review of efficacy and safety. The authorisation of milgamma is based primarily on the medicinal product milgamma mono 300, which contains the same active substance and has been authorised in Germany for more than 10 years. This SwissPAR refers to the authorisation of the foreign comparator medicinal product milgamma mono 300.

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6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for milgamma was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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milgamma®

The efficacy and safety of milgamma have only been summarily reviewed by Swissmedic. The authorisation of milgamma is based on milgamma mono 300, date of revision of the text October 2019, which contains the same active substance and is authorised in Germany.

Composition

Active substances

Benfotiamine.

Excipients

Microcrystalline cellulose, talc, povidone K30, colloidal silica anhydrous, long-chain partial glycerides, croscarmellose sodium, hypromellose 15 mPas, titanium dioxide, macrogol 3350, hypromellose 3 mPas, hypromellose 6 mPas, hypromellose 50 mPas, saccharin sodium.
1 film-coated tablet contains 0.634 mg sodium.

Pharmaceutical form and active substance quantity per unit

1 milgamma film-coated tablet contains 300 mg benfotiamine (lipid-soluble vitamin B_1 derivative) as active substance.
White, oblong film-coated tablet with a score line.
The film-coated tablet can be divided into equal doses.

Indications/Uses

Treatment of disorders responding to administration of vitamin B_1, such as:
- treatment and prophylaxis of vitamin B_1 deficiency that cannot be corrected by dietary means;
- treatment of neurological disorders associated with vitamin B_1 deficiency, such as alcoholic or diabetic polyneuropathy, which can manifest as sensory disturbances (e.g. pain, tingling, numbness) in the extremities;
- treatment of cardiovascular disease associated with vitamin B_1 deficiency in people with diabetes mellitus.

milgamma is used in adults.

Dosage/Administration

The appropriateness of treatment with and/or preventive use of milgamma must be reviewed by a physician three to four weeks after the start of treatment and at regular intervals thereafter.
For severe vitamin B_1 deficiency, intravenous administration of vitamin B_1 may initially be required.

Usual dosage

Prevention of vitamin B_1 deficiency:
Generally, one-half to 1 film-coated tablet (150-300 mg) daily.

Treatment of vitamin B_1 deficiency:
1 film-coated tablet (300 mg) daily.

Treatment of neurological disorders (polyneuropathies) and cardiovascular disorders associated with vitamin B_1 deficiency:
The recommended starting dose is 1 to 2 film-coated tablets (300–600 mg) daily for at least 3 weeks. For continuation of treatment, one-half to 1 film-coated tablet (150–300 mg) daily.

The duration of use depends on the therapeutic outcome.
For the treatment of neuropathies, milgamma should initially be taken over a period of at least 3 weeks. Thereafter, further treatment according to the therapeutic outcome. If no or too little effect is apparent after four weeks, treatment of the symptoms should be reviewed.

Special dosage instructions
Patients with hepatic disorders
The safety and efficacy of milgamma have not been investigated in patients with hepatic disorders. No data are available.

Patients with renal disorders
No dose adjustment is required in patients with renal disorders.

Elderly patients
In elderly patients, no dose adjustment is required.

Children and adolescents
milgamma must not be used in children and adolescents, as its use and safety in this age group have not been studied. No data are available.

Contraindications

Hypersensitivity to the active substance or to any of the excipients of milgamma.

Warnings and precautions

milgamma contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Interactions

Thiamine is inactivated by 5-fluorouracil, since 5-fluorouracil competitively inhibits the phosphorylation of thiamine to thiamine pyrophosphate.

Pregnancy, lactation

Pregnancy

During pregnancy, the recommended daily allowance for vitamin B_1 is 1.2 mg in the 2nd trimester and 1.3 mg in the 3rd trimester. The recommended daily allowance (RDA) for thiamine in pregnant and breast-feeding women is generally obtained from food.
There are no clinical data on use in pregnant women and no adequate animal studies with regard to the effect on pregnancy, embryonic development, fetal development and/or postnatal development. Therefore, at doses exceeding the RDA (recommended daily dietary allowance), caution should be exercised when used during pregnancy.

Lactation

During breast-feeding, the recommended daily allowance for vitamin B_1 is 1.3 mg. Vitamin B_1 is excreted in human milk.

Effects on ability to drive and use machines

No special precautions are required.

Undesirable effects

The undesirable effects are listed by MedDRA system organ classes and frequency according to the following convention:
"very common" (≥1/10)
"common" (≥1/100, <1/10)

“uncommon” (≥1/1000, <1/100)
“rare” (≥1/10,000, <1/1000)
“very rare” (<1/10,000)
“not known” (cannot be estimated from the available data)

Immune system disorders
Not known: hypersensitivity reactions (urticaria, exanthem).

Gastrointestinal disorders
Not known: gastrointestinal disturbance (nausea or other gastrointestinal complaints).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

To date, there have been no reports of overdose with oral use as stated, due to the large therapeutic index.

Properties/Effects

ATC code

A11DA03

Mechanism of action

Vitamin B_1 is an essential active substance. The lipid-soluble prodrug, benfotiamine, is converted to biologically active thiamine pyrophosphate (TPP) in the body. TPP intervenes in important functions of carbohydrate metabolism. Thiamine pyrophosphate acts as a coenzyme in the conversion of pyruvate to acetyl CoA and with transketolase in the pentose phosphate cycle. It also acts in the conversion of alpha-ketoglutarate to succinyl CoA in the citric acid cycle. Due to close links in metabolism, there are interactions with the other vitamins from the B-complex.
Cocarboxylase is, among other things, a coenzyme of pyruvate dehydrogenase, which plays a key role in oxidative glucose degradation. Since energy production in the nerve cells is mainly due to

oxidative glucose degradation, adequate supply of thiamine is essential for nerve function. When glucose levels are elevated, there is an increased need for thiamine.
The absence of sufficient amounts of cocarboxylase in the blood leads to accumulation of intermediate degradation products such as pyruvate, lactate and ketoglutarate in the blood and tissues, to which the muscles, myocardium and CNS are particularly sensitive. Benfotiamine inhibits the accumulation of these toxic substances.
To determine vitamin B_1 status, measurements of thiamine diphosphate-dependent enzyme activities in erythrocytes, such as transketolase (ETK) and the extent of their activation capacity (α-ETK activation coefficient) are suitable. Concentrations for ETK in plasma are between 2 and 4 µg/100 mL.

Pharmacodynamics

See Mechanism of action.

Clinical efficacy

No data.

Pharmacokinetics

Absorption

Vitamin B_1 is present in most foods in the biologically active form as thiamine pyrophosphate. For absorption, the phosphate moiety on the intestinal wall has to be cleaved by the pyrophosphatases present there. For the absorption of thiamine, a dose-dependent dual transport mechanism is assumed, viz. active absorption at an administered amount of up to 2 µmol and passive diffusion at higher doses.
Approximately 1 mg of thiamine is degraded daily in the body. Excess thiamine is excreted via the urine.
Following oral administration of the lipid-soluble prodrug benfotiamine, dephosphorylation occurs in the intestine by phosphatases to form fat-soluble S-benzoylthiamine (SBT). This is better absorbed than water-soluble thiamine derivatives and reaches the cell interior from circulating blood. Here, enzymatic debenzoylation takes place to form thiamine, which is subsequently converted by thiamine kinase to the active coenzyme form (cocarboxylase, synonym: thiamine diphosphate). Significantly higher concentrations of thiamine and the active coenzymes are reached intracellularly with benfotiamine than with orally administered water-soluble thiamine derivatives.
Absorption of benfotiamine is dose-proportional since, in contrast to thiamine, the substance is not subject to saturation kinetics due to its lipid solubility.

It has been demonstrated that thiamine pyrophosphate and triphosphate, which are biologically active coenzymes, are formed from benfotiamine in the body. Using whole-animal autoradiography, particularly high radioactivity was detected with labelled benfotiamine in the brain, heart muscle and diaphragm.

Distribution

See Absorption.

Metabolism

See Absorption.

Elimination

See Absorption.

Other information:
The kinetic properties of the lipid-soluble prodrug benfotiamine differ significantly from water-soluble thiamine derivatives. The much higher bioavailability of benfotiamine compared to thiamine mononitrate (Bitsch, 1990) has been proven Significantly higher thiamine levels in the plasma, haemolysate and erythrocytes are also achieved with benfotiamine under physical stress than with water-soluble thiamine derivatives, as a bioavailability study on 20 athletes has shown (Beuker, 1996). After administration of an equimolar amount, an approximately 5-fold higher bioavailability was established for benfotiamine compared to thiamine mononitrate. Peak plasma concentration (c_{max}) was up to 16-fold higher (internal company data, 1996).

Preclinical data

Acute, subchronic and chronic toxicity
In animals, very high doses of vitamin B_1 cause bradycardia. Symptoms of blockade of the autonomic ganglia and muscle end plates also occur.
In animal trials on chronic toxicity, no pathological organ changes were observed at doses of 100 mg/kg benfotiamine.

Mutagenicity and carcinogenicity
No mutagenic effects of vitamin B_1 are to be expected under conditions of clinical use.
No long-term animal studies are available on the tumorigenic potential of vitamin B_1.

Reproductive toxicity

Vitamin B_1 is actively transported to the fetus. Concentrations in fetuses and neonates exceed maternal vitamin B_1 concentrations.

High doses of vitamin B_1 have been insufficiently studied in animal trials.

Other information

Shelf life

Do not use this medicine after the expiry date “EXP” stated on the pack.

Special precautions for storage

Do not store above 30 °C.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

Medicines should not be disposed of via wastewater or household waste. This measure will help protect the environment.

Authorisation number

68695 (Swissmedic)

Packs

milgamma: 10, 30, 60, 90 and 100 film-coated tablets [D]

Marketing authorisation holder

MARAS AG, 6330 Cham

Date of revision of the text

Date of revision of the text - Foreign comparator medicinal product: October 2019
With safety-relevant additions by Swissmedic: December 2022