Date: 24 July 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Triogen

International non-proprietary name: trientini dihydrochloridum
Pharmaceutical form: capsule, hard
Dosage strength: 250 mg
Route(s) of administration: oral
Marketing Authorisation Holder: IDEOGEN AG
Marketing Authorisation No.: 67431
Decision and Decision date: approved on 28 May 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
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)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 of the TPA.
The Orphan Status was granted on 12 April 2019.

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

2.2 Indication and Dosage

2.2.1 Requested Indication

For the treatment of copper storage disease (Wilson's disease) in patients intolerant of D-penicillamine therapy

2.2.2 Approved Indication

For the treatment of Wilson's disease in patients intolerant of D-penicillamine therapy.

2.2.3 Requested Dosage

For oral use.
Usual dosage
Adults (including elderly patients): 1.0-2.0 grams (4-8 capsules) daily in 2 to 4 divided doses preferably 30 minutes to 1 hour before meals.
Children and adolescents
The dose is lower than for adults and depends on age and body weight. The dose should be adjusted according to clinical response. 0.5-1.25 grams (2-5 capsules) have been used at initiation of therapy.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	25 January 2019
Formal control completed	3 May 2019
List of Questions (LoQ)	16 August 2019
Answers to LoQ	14 October 2019
Predecision	15 January 2020
Answers to Predecision	2 March 2020
Final Decision	28 May 2020
Decision	approval

For the application for the authorisation of the medicinal product Triogen capsules, Swissmedic has reviewed the quality exclusively on the basis of primary data. The authorisation of Triogen capsules is based primarily on the medicinal product Trientine dihydrochloride capsules 300 mg, which contains

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

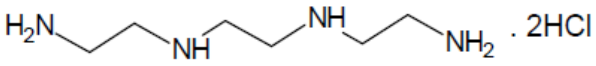
the same active substance and has been authorised in the UK for more than 10 years. Apart from those sections for which Swissmedic has conducted an independent scientific review, this SwissPAR refers to the authorisation of the foreign comparator medicinal product Trientine dihydrochloride capsules 300 mg.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Quality Aspects

3.1 Drug Substance

INN: Trientine
Chemical name: 1,2-Ethanediamine, N,N'-bis(2-aminoethyl)-, dihydrochloride
Molecular formula: $C_6H_{18}N_4 \cdot 2\ HCl$
Molecular mass: 219.16
Molecular structure:



Trientine is a white to pale yellow hygroscopic crystalline powder. Trientine is freely soluble in water. Trientine does not have a chiral centre. Polymorphism has been observed.
The drug substance is manufactured by a multiple-step chemical synthesis with final isolation by crystallisation.
The structure of trientine has been fully elucidated using several spectroscopic techniques.
The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities, and water content.
Appropriate stability data have been presented and justify the established re-test period.

3.2 Drug Product

The finished product is available as immediate-release hard gelatin capsules. Each capsule contains 250 mg of trientine dihydrochloride. The hard gelatin capsules are opaque brown and printed with “HP551” in black.
The composition of the drug product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
Satisfactory validation data pertaining to the commercial manufacturing process are provided.
The drug product specification covers appropriate parameters for this dosage form and includes relevant physicochemical, identification, assay and purity tests. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
The drug product is packaged in HDPE bottles with child-resistant closures.
Appropriate stability data have been generated in the packaging material intended for commercial use and following relevant international guidelines. The data show good stability of the finished product and support the proposed shelf life.

3.3 Quality Conclusions

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

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Nonclinical Aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has not reviewed any nonclinical data for the authorisation of Triogen capsules. The approval of Triogen capsules is based on the medicinal product Trientine dihydrochloride capsules 300 mg, which contains the same active substance and has been authorised in the UK for more than 10 years.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Clinical and Clinical Pharmacology Aspects

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

The submitted bioequivalence study can be accepted for the bridging between the proposed product Triogen capsules and the product authorised in the UK (Trientine dihydrochloride capsules 300 mg, from the company Univar, Rotterdam, Netherlands). In view of the demonstrated comparable bioavailability of the parent substance and the supportive data for the metabolite N1-acetyl-triethylenetetramine, the adaptation of the dosage suggested in the Information for healthcare professionals can also be accepted.

5.1 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Triogen capsules 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Triogen 250 mg

The efficacy and safety of Triogen 250 mg have only been summarily reviewed by Swissmedic.
The authorisation of Triogen 250 mg is based on Trientine Dihydrochloride capsules 300 mg, date of revision of the text November 2019, which contains the same active substance(s) and is authorised in the United Kingdom.

Composition

Active substances

Trientine dihydrochloride

Excipients

Contents of capsule:
Silica colloidal anhydrous, stearic acid.
Capsule shell:
gelatine, purified water, sodium lauryl sulphate correspondinf to 0.0048 mg sodium, red iron oxide (E172), yellow iron oxide (E172), titaniumdioxide (E171).
Printing ink:
shellac, butyl alcohol, propylene glycol, potassium hydroxide, black iron oxide (E172).

Pharmaceutical form and active substance quantity per unit

Hard capsule with a brown, opaque cap with “HP551” printed on in black and a brown, opaque main portion with “HP551” printed on in black.
Each capsule contains 250 mg trientine dihydrochloride, corresponding to 167 mg base.

Indications/Uses

For the treatment of Wilson’s disease in patients intolerant of D-penicillamine therapy.

Dosage/Administration

For oral use.

Usual dosage

Adults (including elderly): 1.0-2.0 grams (4-8 capsules) daily in 2 to 4 divided doses preferably 30 minutes to 1 hour before meals.

Children and adolescents

The dose is lower than for adults and depends on age and body weight. The dose should be adjusted according to clinical response. 0.5-1.25 grams (2-5 capsules) have been used at initiation of therapy.

Contraindications

No Information.

Warnings and precautions

Trientine is not indicated as an alternative to D-Penicillamine in the treatment of rheumatoid arthritis or cystinuria. Penicillamine-induced systemic lupus erythematosus may not resolve on transfer to trientine. Trientine is a chelating agent which has been found to reduce serum iron levels possibly reducing its absorption.
Iron supplementation may be necessary in some cases and should be administered at a different time of the day to trientine.
There is no evidence that calcium or magnesium antacids alter the efficacy of trientine but it is good practice to separate their administration. (i.e. antacids should be taken after meals).
There is no advantage in using trientine and penicillamine in combination.
There have been reports of neurological deterioration in Wilson's Disease patients treated with copper chelators including trientine. It is possible this effect may be more evident in patient with pre-existing neurological symptoms. It is recommended to monitor patients closely for such signs and symptoms and to consider a titrated increase in dose to reach the recommended therapeutic dose.
Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, i.e. It is almost "sodium-free".

Interactions

Effect of Triogen 250 mg on other medicinal products

Trientine has been found to reduce serum iron levels.

Pregnancy, lactation

Pregnancy

The product should be used in pregnancy only after careful consideration of the benefits compared with the risks of treatment in the individual patient. Factors which need to be borne in mind include the risks associated with the disease itself, the risk of those alternative treatments which are available and the possible teratogenic effects of trientine.
The pregnancy should be monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy.
The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range. Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate.

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

Undesirable effects after market launch

Nausea on initial treatment and occasionally skin rash can occur. Duodenitis and severe colitis have been reported. Very rarely anaemia.
There have been reports of neurological deterioration in Wilson's Disease patients treated with copper chelators including trientine, with symptoms of, for example, dystonia, rigidity, tremor and dysarthria.

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 adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Occasional cases of trientine overdose have been reported. In cases up to 20 g of trientine base there were no apparent adverse effects reported. A large overdose of 40 g of trientine base resulted in self-limiting dizziness and vomiting with no other clinical sequelae or significant biochemical abnormalities reported. There is no antidote for trientine acute overdose.

Properties/Effects

ATC code

A16AX12

Mechanism of action

Trientine dihydrochloride is a copper-chelating agent which aids the elimination of copper from the body by forming a stable soluble complex that is readily excreted from the kidney.

Pharmacodynamics

Not applicable.

Clinical efficacy

Not applicable.

Pharmacokinetics

No information.

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

No information.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture.
Keep out of the reach of children.

Authorisation number

67431 (Swissmedic).

Packs

HDPE-bottle with 100 capsules [B].

Marketing authorisation holder

Ideogen AG, Freienbach.

Date of revision of the text

Foreign reference/comparator medicinal product: November 2019.
Without safety-relevant additions by Swissmedic: December 2019.