swissmedic

Date: 1 March 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Spaverin

International non-proprietary name: drotaverine hydrochloride
Pharmaceutical form: tablets
Dosage strength(s): 80 mg, 40 mg
Route(s) of administration: oral
Marketing authorisation holder: Target BioScience AG
Marketing authorisation no.: 68410
Decision and decision date: approved on 30 January 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.

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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
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 drotaverine hydrochloride in the above-mentioned medicinal product.

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

2.2 Indication and dosage

2.2.1 Requested indication

- *Smooth muscle spasms in diseases of the hepato-biliary system:* cholecystolithiasis, cholangiolithiasis, cholecystitis, pericholecystitis, cholangitis, papillitis.
- *Smooth muscle spasms of the urogenital system:* nephrolithiasis, ureterolithiasis, pyelitis, cystitis, tenesmus of urinary bladder.
- *As adjuvant:*
- Smooth muscle spasm of the gastrointestinal system: ventricular and duodenal ulcer, gastritis, spasm of the pylorus or cardia, enteritis, colitis, irritable colon syndrome predominantly with constipation or with abdominal distension.
- Tension-type headache.
- Gynaecological disease: dysmenorrhoea.

2.2.2 Approved indication

Adult patients:
Symptomatic treatment of gastrointestinal complaints (pain, cramps) in the context of functional disorders of the gastrointestinal tract.

2.2.3 Requested dosage

Summary of the requested standard dosage:

Adults: The recommended daily dose is 120-240 mg (in 2-3 separate doses).
Children and adolescents:
No clinical studies have been performed with drotaverine in paediatric populations.
If the use of Spaverin tablet is necessary:
Children from 6 to 12 years of age: the daily dose should not be more than 80 mg in 2 separate doses.
Children above 12 years of age: the daily dose should not be more than 160 mg in 2-4 separate doses.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	8 March 2021
Formal control completed	14 June 2021
List of Questions (LoQ)	8 October 2021
Response to LoQ	13 February 2021
Preliminary decision	13 May 2022
Response to preliminary decision	12 June 2022
2nd Preliminary decision	2 September 2022
Response to 2nd Preliminary decision	1 November 2022
Final decision	30 January 2023
Decision	approval

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3 Quality aspects

3.1 Drug substance

INN: Drotaverine Hydrochloride

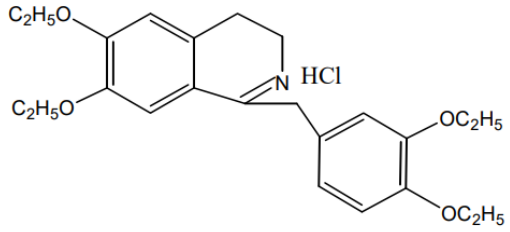
Chemical name:

1-(3,4-Diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride

Molecular formula: $C_{24}H_{31}NO_4.HCl$

Molecular mass: 433.97

Molecular structure:



Physico-chemical properties:

Almost light yellow to yellow with greenish tinge, odourless, crystalline powder, freely soluble in chloroform, soluble in 95% alcohol, sparingly soluble in water, non-chiral, pH 3.3 to 5.5, melting range 208° to 211°C.

Synthesis:

Chemical synthesis involving several steps.

Specification:

In order to ensure a consistent quality of the drug substance, the specifications include relevant test parameters as recommended by the relevant ICH guidelines. 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 tight packaging proposed in the application.

3.2 Drug product

Description and composition:

Drotaverine hydrochloride immediate release tablets are provided in two strengths. Drotaverine hydrochloride 40 mg tablet is a yellow, round, biconvex tablet imprinted “40” on one side.

Drotaverine hydrochloride 80 mg tablet is a yellow, round, biconvex tablet imprinted “80” on one side and scored on the other side.

The tablets consist of the pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, povidone, maize starch, magnesium stearate and talc.

Tablets are packaged in transparent PVC / aluminium blisters.

Pharmaceutical development:

Tablets were chosen to adequately administer the active ingredient, involving common excipients for immediate release dosage forms.

Manufacture:

The tablets are manufactured by wet granulation, drying of the granules and subsequent compression of the final tablet blend. Process parameters and in-process controls are defined in order to ensure a consistent quality of the tablets.

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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 physico-chemical characteristics, identification of the drug substance and assay and purity tests. The corresponding test procedures have been validated.

Container closure system:

Tablets are packaged in blisters composed of transparent PVC and aluminium foil.

Stability:

Stability data have been generated for the product packaged in blisters, according to the relevant international guidelines. Based on the stability studies, a shelf-life of 60 months was requested for drotaverine hydrochloride tablets. The storage recommendation is “Do not store above 30°C”, and to keep the product in its original container.

3.3 Quality conclusions

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

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4 Non-clinical aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has not assessed the primary data relating to non-clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority in Hungary. The active substance, drotaverine hydrochloride, has been authorised in Hungary for more than 10 years.

5 Clinical and clinical pharmacology aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority in Hungary. The active substance, drotaverine hydrochloride, has been authorised in Hungary for more than 10 years.

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.

7 Appendix

Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Spaverin was submitted with the application 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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Spaverin®

The efficacy and safety of Spaverin have only been assessed briefly by Swissmedic. The authorisation of Spaverin is based on the information as at February 2018, whereby the product contains the same active substance and is authorised in Hungary.

Composition

Active substances

Drotaverine hydrochloride.

Excipients

Lactose monohydrate, microcrystalline cellulose, Povidone K-29/32, maize starch, magnesium stearate, talc.

Spaverin 40 mg: 20 mg lactose monohydrate per tablet.
Spaverin 80 mg: 40 mg lactose monohydrate per tablet.

Pharmaceutical form and active substance quantity per unit

Tablets containing 40 mg or 80 mg drotaverine hydrochloride.
The 80 mg tablets are divisible.

Indications/Uses

Adult patients:
Symptomatic treatment of gastrointestinal complaints (pain, cramps) in the context of functional disorders of the gastrointestinal tract

Dosage/Administration

Adults
The usual dose is 120 to a maximum of 240 mg per day (split into 2-3 doses). A dose of 240mg/day should not be exceeded.

Special dosage instructions

Children and adolescents
Spaverin is not authorised for use in children and adolescents. Only limited data are available on the efficacy and safety of the use of drotaverine in children and adolescents aged six years and over. Use in children under the age of six years is contraindicated (see “Contraindications” section).

Patients with impaired hepatic or renal function
There are insufficient data on patients with impaired hepatic or renal function. This product should be used with caution in these patients. The use of Spaverin is contraindicated in patients with severely impaired hepatic or renal function (see “Contraindications” section).

Contraindications

- Hypersensitivity to the active substance or one of the excipients
- Severely impaired hepatic function
- Severely impaired renal function
- NYHA III-IV heart failure with reduced ejection fraction
- Children under the age of six years
- Paralytic or mechanical ileus
- Stenosis of the gastrointestinal tract

Warnings and precautions

Use in patients with heart failure, hypotonia or orthostatic dysregulation
Drotaverine has vasodilating properties. There are no or insufficient data on patients with known heart failure or a tendency to hypotonia/orthostatic dysregulation. The use of Spaverin in these patients is not recommended.
The use of Spaverin is contraindicated in patients with advanced heart failure (see “Contraindications” section).

Every Spaverin 40 mg or 80 mg tablet contains 20 mg or 40 mg lactose monohydrate respectively. Patients with rare hereditary conditions of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interactions

Phosphodiesterase inhibitors, e.g. papaverine, reduce the antiparkinson effect of levodopa. The concomitant use of drotaverine and levodopa reduces the antiparkinson effect of levodopa and can lead to a deterioration in the symptoms of Parkinson’s disease.

Pregnancy, lactation

Pregnancy
Animal studies have provided no indication of direct adverse health effects in relation to pregnancy, embryonic/foetal development, birth or postnatal development (see “Preclinical data”). Drotaverine

may promote cervical dilation. Drotaverine did not have a negative effect on the mother or the newborn when administered intravenously or intramuscularly during the birth. The clinical effect on early pregnancy and on the unborn child in humans is not known. Spaverin should not be used during pregnancy.

Lactation

Due to the lack of sufficient study results, use while breastfeeding is not recommended.

Fertility

There are no data on human fertility.

Effects on ability to drive and use machines

No relevant studies have been conducted. The use of Spaverin may cause undesirable effects such as dizziness and vertigo. Affected patients should refrain from driving a vehicle or using machines until the undesirable effect has subsided.

Undesirable effects

Possible adverse reactions associated with the use of drotaverine identified as part of clinical trials are listed below by system organ class.

The following frequency categories are used:
“Very common” (≥1/10), “common” (≥1/100, <1/10), “uncommon” (≥1/1,000, <1/100), “rare” (≥1/10,000, <1/1,000), “very rare” (<1/10,000), “not known” (frequency cannot be estimated from the available data).

Immune system disorders

Rare: allergic reactions (angioedema, urticaria, skin rash, itching)

Vascular disorders

Rare: palpitations, reduced blood pressure

Not known: priapism

Nervous system disorders

Rare: headache, dizziness, insomnia

Gastrointestinal tract disorders

Rare: nausea, constipation

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

Overdose

Several deaths have been reported in connection with drotaverine intoxication. Overdose of drotaverine may lead to (fatal) cardiac arrhythmias.
In one study, 86 cases of drotaverine intoxication were described in more detail as being associated with suicidal intent. The average dose of drotaverine in these cases was around 46 mg/kg body weight. Cardiac arrhythmias were observed in around 45% of these patients and measures to support the cardiovascular system (atropine, dobutamine) were required in around 35%. In the event of drotaverine intoxication, medical advice should be sought immediately and suitable clinical/intensive care measures initiated.

Properties/Effects

ATC code

A03AD02 Drugs for gastrointestinal disorders

Mechanism of action and pharmacodynamics

Drotaverine is an isoquinoline derivative that exerts its spasmolytic effect directly on the smooth musculature. The inhibition of the phosphodiesterase enzyme and resulting increase in cAMP levels are key to its mechanism of action, which helps relax the smooth musculature by deactivating the myosin light-chain kinase (MLCK) enzyme.
In vitro, drotaverine is a specific inhibitor of phosphodiesterase-IV (PDE IV) without significantly blocking the PDE III and PDE V isoenzymes.

Pharmacodynamics

Clinical efficacy

No information.

Pharmacokinetics

Absorption

Drotaverine is absorbed quickly following oral administration, whereby the maximum plasma concentration is achieved 1-3 hours after administration.

Distribution

Drotaverine is bound 95-98% to albumin, and alpha globulin and beta globulin. The highest serum concentrations were achieved between 45 and 60 minutes after oral administration.

Metabolism

Following first pass metabolism in the liver, 65% of the administered dose reaches the systemic circulation unchanged. Drotaverine is metabolised in the liver.

Elimination

The biological half-life is 8-10 hours. Within 72 hours, it is practically completely eliminated from the body, approx. 50% in the urine and 30% in the faeces.
Drotaverine is primarily excreted in the form of metabolites and cannot be detected unchanged in the urine.

Preclinical data

Based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity and carcinogenic potential, the non-clinical data reveal no special hazard for humans.

- Based on in vitro and in vivo studies, drotaverine did not cause a delay in ventricular repolarisation.
- In in vitro and in vivo genotoxicity studies (e.g. Ames test, mouse lymphoma assay, micronucleus assay), drotaverine showed no indication of genotoxicity.
- Drotaverine had no impact on fertility in rats and on embryonic/foetal development in rats and rabbits.

It has been observed that drotaverine acts as a cytostatic agent in various human tumour cell lines and non-malignant mouse fibroblasts. In SRB assays, EC_{50} values of up to 3.0 mM were observed for human HT-29 colorectal cancer cells. The clinical consequences of this effect are not known and no relevant undesirable effects in children, adolescents or adults have been observed during five decades of use in humans.

Other information

Shelf life

Do not use this medicinal product after the date marked “EXP” on the pack.

Special precautions for storage

Do not store above 30°C. Store in the original packaging.
Keep out of the reach of children.

Authorisation number

68410

Packs

Spaverin 40 mg: pack of 20 tablets [B].

Spaverin 80 mg: pack of 10 or 20 divisible tablets [B].

Marketing authorisation holder

Target BioScience AG, CH-8803 Rüschlikon.

Date of revision of the text

Foreign comparator medicinal product: February 2018

With safety-related additions by Swissmedic: January 2023