swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Levocalm

International non-proprietary name: levodropropizine
Pharmaceutical form: syrup
Dosage strength(s): 30 mg/5 mL
Route(s) of administration: oral
Marketing authorisation holder: Gebro Pharma AG
Marketing authorisation no.: 69413
Decision and decision date: approved on 18 July 2024

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

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)
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)

2 Background information on the procedure

2.1 Applicant's request(s)

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

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

2.2 Indication and dosage

2.2.1 Requested indication

Symptomatic treatment of non-productive cough.

2.2.2 Approved indication

Symptomatic treatment of non-productive cough in adults, adolescents and children from the age of 2 years. The maximum duration of treatment without medical consultation is 7 days.

2.2.3 Requested dosage

The medicinal product is used 3 times daily at intervals of at least 6 hours.
Children under 2 years old: Levocalm should not be used in children under the age of 2 years.
Children over 2 years old: 10-20 kg: 3 mL of syrup 3 times daily;
20-30 kg: 5 mL of syrup 3 times daily.
Adults: 10 mL of syrup up to 3 times daily.
The maximum duration of treatment without medical consultation is 7 days.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

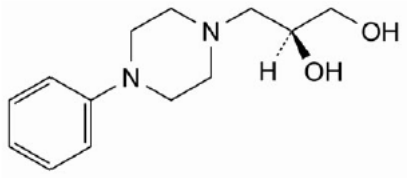
Application	1 May 2023
Formal objection	15 May 2023
Response to formal objection	1 June 2023
Formal control completed	6 June 2023
List of Questions (LoQ)	28 September 2023
Response to LoQ	15 November 2023
Preliminary decision	12 February 2024
Response to preliminary decision	25 April 2024
Labelling corrections	30 May 2024
Response to labelling corrections	4 June 2024
Final decision	18 July 2024
Decision	approval

For the application for the authorisation of the medicinal product Levocalm, Swissmedic has reviewed only the quality on the basis of primary data. The authorisation of Levocalm is based primarily on the medicinal product Levotuss 30 mg/5 mL syrup, which contains the same active substance and has been authorised in Italy 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, Levodropropizine ELC 30 mg/5 mL syrup.

3 Quality aspects

3.1 Drug substance

INN: Levodropropizine
Molecular formula: $C_{13}H_{20}N_2O_2$
Molecular mass: 236.3
Molecular structure:



The specification complies with Ph. Eur. Monograph Levodropropizine.

An appropriate retest period has been established.

3.2 Drug product

Levodropropizine 30 mg/5 mL syrup, containing the active substance levodropropizine, can be described as clear, light yellowish syrup with a raspberry flavour.

The manufacturing process is a standard process of dissolving the drug substance and the excipients in water. The aqueous solution obtained is filtered and filled into glass bottles of different volumes.

For the control of the finished product, adequate tests and criteria for release and at shelf-life have been established.

The packaging consists of an amber glass bottle, type III, with a polypropylene (PP) / polyethylene (PE) or polypropylene (PP) child-proof cap with a liner made of polyethylene (PE) and a polypropylene (PP) measuring cup graduated in mL.

Appropriate stability data have been presented. Based on these results, a satisfactory shelf-life of 36 months has been established.

3.3 Quality conclusions

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

4 Nonclinical aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has only reviewed the nonclinical overview. The authorisation of Levocalm is based on the medicinal product Levotuss 30 mg/5 mL syrup, which contains the same active substance and has been authorised in Italy for more than 10 years.

5 Clinical aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has conducted only a summary review of efficacy and safety. The authorisation of Levocalm is based on the medicinal product Levotuss 30 mg/5 mL syrup, which contains the same active substance and has been authorised in Italy 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

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Levocalm 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.

Levocalm 30 mg / 5 ml, syrup

The efficacy and safety of Levocalm have only been summarily reviewed by Swissmedic. The authorisation of Levocalm is based on Levodropropizine ELC 30 mg/5 ml syrup, Date of revision of the text December 2021, which contains the same active substance and is authorised in Malta.

Composition

Active substances

Levodropropizine

Excipients

Citric acid monohydrate, sodium hydroxide (corresponding to max. 11.45 mg sodium), 3 g sucrose, flavouring (raspberry flavour, contains 0.98 mg ethanol), purified water per 5 ml syrup.

Pharmaceutical form and active substance quantity per unit

30 mg levodropropizine per 5 ml syrup.

Indications/Uses

Symptomatic treatment of non-productive cough in adults, adolescents and children from the age of 2 years. The maximum duration of treatment without medical consultation is 7 days.

Dosage/Administration

Dosage

The medicine is used three times a day at intervals of at least 6 hours.
If the cough persists after seven days of treatment with Levocalm, treatment should not be continued until a doctor has been consulted.
A cough is a symptom, the cause of which should be investigated and treated.

Dosage for adults and adolescents aged 12 years and over

Adults and adolescents take 10 ml syrup (equivalent to 60 mg levodropropizine) as a single dose using the measuring cup. This single dose can be taken up to three times a day. However, at least 6 hours must have passed before the next dose is taken.

Dosage for children

Children aged between 2 and 11 years generally receive a total daily dose of 0.5 ml syrup per kilogram (kg) of body weight (equivalent to 3 mg levodropropizine per kg body weight). The total daily dose is divided into three individual doses with an interval of at least 6 hours.

The following table can serve as a guide for the single and total daily dose:

Body weight of the patient	**Single dose**	**Total daily dose in 24 hours**
up to 12 kg	2 ml	up to 6 ml
12.5 to 18 kg	3 ml	up to 9 ml
18.5 to 24 kg	4 ml	up to 12 ml
24.5 to 30 kg	5 ml	up to 15 ml
30.5 to 36 kg	6 ml	up to 18 ml
36.5 to 42 kg	7 ml	up to 21 ml

Mode of administration

Levocalm is to be taken orally. The syrup bottle comes with a measuring cup that can be used to measure 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml and 10 ml.
Since only incomplete information is available on the influence of meals on the absorption of Levocalm, it is recommended not to take Levocalm together with a meal.

To open the bottle, press the cap down and turn it anti-clockwise.

Special dosage instructions

Patients with hepatic / renal disorders

The use of Levocalm in individuals with severely impaired renal function (creatinine clearance < 35 ml/min) is not recommended. Use is contraindicated in individuals with severely impaired hepatic function (see section "Contraindications").

Elderly patients (≥65 years old)

The fact that no significant change in the pharmacokinetic profile of levodropropizine was observed in elderly patients indicates that an adjustment of the dose or the intervals between successive doses is probably not necessary in the elderly. Nevertheless, levodropropizine should be used with caution in this patient group, as there are indications of an altered sensitivity of elderly patients to numerous medicinal products.

Contraindications

- Hypersensitivity to the active substance or any of the other ingredients

- Children under the age of 2
- Pregnancy and breastfeeding (see section "Pregnancy, lactation")
- Productive cough / bronchorrhoea
- Reduced mucociliary function (Kartagener's syndrome, ciliary dyskinesia)
- Severe impairment of liver function.

Warnings and precautions

Caution is advised when using sedative medicinal products and substances at the same time.

In patients with a productive cough, the simultaneous administration of mucolytic or secretolytic substances can lead to an undesirable build-up of secretions in the bronchi. This increases the risk of a respiratory infection and bronchospasm.

This medicinal product contains 6 g sucrose per 10 ml. This must be taken into account in patients with diabetes mellitus.
Patients with the rare hereditary fructose/galactose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not use this medicinal product.

Interactions

In pharmacological studies in humans, the combination with benzodiazepines did not change the EEG pattern.

Studies conducted with other medicinal products

Clinical studies showed no interaction with medicinal products for the treatment of bronchial diseases, such as beta-2-sympathomimetics, methylxanthines and derivatives, corticosteroids, antibiotics, mucoregulators and antihistamines.

Pregnancy, lactation

Pregnancy

As the active substance can cross the placental barrier in animal experiments, the medicinal product is contraindicated in women who wish to become pregnant or are pregnant because the safety of its use has not been documented (see "Contraindications").

Lactation

As the active substance has been detected in breast milk in animal experiments, the use of the medicinal product during breastfeeding is contraindicated (see "Contraindications").

Fertility

Studies investigating the potential teratogenic effects of levodropropizine and its effects on fertility and reproduction, as well as peri- and postnatal studies, did not reveal any particular toxic effects of the medicinal product.

Effects on ability to drive and use machines

No corresponding studies have been performed. The medicine may cause drowsiness (see section "Undesirable effects") and thus impair the ability to drive a vehicle or operate machinery.

Undesirable effects

Summary of the safety profile

Post-marketing data on levodropropizine preparations in over 30 countries worldwide indicate that adverse reactions occur very rarely. Most adverse reactions were not serious and symptoms resolved after discontinuation of treatment or, in some cases, after targeted medicinal treatment. Serious cases included skin reactions (urticaria, itching), cardiac arrhythmia, hypoglycaemic coma and allergic/anaphylactoid reactions with oedema, dyspnoea, vomiting and diarrhoea. A single case of epidermolysis in an elderly patient took a fatal course.

List of adverse reactions

The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows:
“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

Not known: eyelid oedema, angioneurotic oedema.

Psychiatric disorders

Very rare : irritability, sleepiness, depersonalisation.

Nervous system disorders

Very rare: dizziness, rotatory vertigo, tremor, paraesthesia.

Not known: tonic-clonic convulsions, petit mal seizure.

Eye disorders

Not known: A single case of mydriasis and one case of bilateral loss of vision were reported. In both cases, the adverse reaction subsided after discontinuation of the medicinal product.

Cardiac disorders

Very rare: palpitations, tachycardia, hypotension.

Not known: cardiac arrhythmia (atrial bigeminus).

Respiratory, thoracic and mediastinal disorders

Very rare: dyspnoea, cough, respiratory oedema.

Gastrointestinal disorders

Very rare: abdominal and lower abdominal pain, nausea, vomiting, diarrhoea.

Not known: glossitis, aphthous fever, cholestatic hepatitis, hypoglycaemic coma.

Skin and subcutaneous tissue disorders

Very rare: urticaria, erythema, exanthema, itching, angioedema, skin reactions.

Not known: A single case of epidermolysis with a fatal outcome has been reported.

Musculoskeletal and connective tissue disorders

Very rare: asthenia, weakness of the lower extremities.

General disorders and administration site conditions

Very rare: allergic and anaphylactic reactions, general malaise.

Not known: generalised oedema, syncope, asthenia.

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

No significant adverse reactions were observed after a single dose of up to 240 mg and 120 mg three times daily for 8 consecutive days. Only one case of overdose is known, which occurred in a three-year-old child who was administered a daily dose of levodropropizine of 360 mg. This resulted in moderate abdominal pain and vomiting, which subsided without consequences.
In the event of an overdose with clinical symptoms, the responsible toxicological centre (Toxinfo Switzerland) should be contacted immediately.

Properties/Effects

ATC code

R05DB27
Pharmacotherapeutic group: Cough and cold remedies: Antitussives, excl. combinations with expectorants: other antitussives.

Mechanism of action

Levodropropizine is produced by stereospecific synthesis and corresponds chemically to the substance (S)-3-(4-phenyl-piperazin-1-yl)-propane-1,2-diol.

The drug has a mainly peripheral tracheobronchial antitussive effect and a bronchospasm-relieving effect.
Levodropropizine acts on the bronchopulmonary system by inhibiting bronchospasm triggered by histamine, serotonin and bradykinin. The bronchospasm induced by acetylcholine is not inhibited by the active substance, which shows the absence of anticholinergic effects.

Pharmacodynamics

With regard to the mechanism of action, the antitussive activity of levodropropizine is attributed to its inhibitory effect on C-fibres. In vitro, levodropropizine inhibits the release of neuropeptides from the C-fibres.
In healthy volunteers, a 60 mg dose reduced the cough induced by a citric acid aerosol for at least 6 hours.

The active substance does not suppress lung function or mucociliary clearance in humans. A recent study showed that levodropropizine has no suppressive effect on the central respiratory regulatory systems in subjects with chronic respiratory insufficiency under spontaneous breathing conditions and during hypercapnic ventilation.

Clinical efficacy

No information.

Pharmacokinetics

Absorption

The oral bioavailability is around 75%. The recovery of radioactivity after oral administration of the product is around 93%.

Distribution

Plasma protein binding is around 11-14%.

Metabolism

Levodropropizine is rapidly distributed throughout the body after oral administration. The half-life is about 1 to 2 hours.

Elimination

Excretion is mainly via the urine, both in unchanged form and in the form of metabolites (as conjugated levodropropizine and as free and conjugated p-hydroxylevodropropizine).

The excretion of the product and its metabolites via the urine amounts to about 35% of the ingested dose over a period of 48 hours. Studies in which the medicinal product was taken repeatedly show that eight days of treatment (three times a day) does not alter the absorption and elimination profile.

No significant changes in the pharmacokinetic profile were observed in children, elderly patients and patients with mild or moderate renal insufficiency.

Preclinical data

The acute oral toxicity is 886.5 mg/kg in rats, 1,287 mg/kg in mice and 2,492 mg/kg in guinea pigs. The therapeutic index in guinea pigs (calculated as LD_{50}/ED_{50} after oral administration) is between 16 and 53, depending on the experimental model of cough induction. Toxicity studies

with repeated oral administration (4 to 26 weeks) showed that the daily dose without toxic effect is 24 mg/kg.

Other information

Shelf life

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

Shelf life after opening

Shelf life after opening: 6 months.

Special precautions for storage

Store at room temperature (15-25°C).
Do not store in the refrigerator.
Do not freeze.
Store in the original amber glass bottle to protect the contents from light.
Keep out of the reach of children.

Authorisation number

69413 (Swissmedic)

Packs

Pack of 120 ml syrup [D]
Pack of 200 ml syrup [D]

Marketing authorisation holder

Gebro Pharma AG, 4410 Liestal

Date of revision of the text

Foreign comparator medicinal product: 12/2021

Without safety-relevant additions by Swissmedic: February 2024