1. NAME OF THE MEDICINAL PRODUCT

Ledermix® paste.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g paste contains: 30.21 mg demeclocycline calcium (equivalent to 30.00 mg demeclocycline hydrochloride) and 10 mg triamcinolone acetonide.
Excipients with known effect: 1 g paste contains 3 mg sodium sulphite anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Paste for use in dental cavities
Ledermix Paste is a greyish-yellow soft paste

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Compound for dental use, prophylaxis or treatment of acute pulpitis and periodontitis.

4.2 Posology and method of administration
Posology
The dosage depends on the nature and scope of use.

Paediatric population

Insufficient data are available for use in children (aged 3 years and older) (see section 4.4).

Method of administration
A: Cases of pulpitis, with exposure of the pulp
Practical procedure:
1st session: If after preparing the cavity and creating the extension and retention element, removal of the carious dentine close to the pulp has resulted in exposure of the pulp, carefully clean the cavity and pulp wound (H_2O_2 3% or physiological NaCl solution). Squeeze a small amount of Ledermix Paste onto a small pellet of cotton wool or felt and apply to the exposed pulp. Seal the cavity with ZnO eugenol or another, tightly sealing, temporary cavity filling material.
2nd session (two to three days later): Vitality test, remove the temporary filling and pellet. Clean the cavity and pulp wound (H_2O_2 3% or physiological NaCl solution). Inspect the pulp wound. If necessary, local anaesthesia. Cap the exposed pulp. Then perform underfilling and final cavity filling in the same session.

B: Cases of pulpitis with closed pulp cavity.
As exposure of the inflamed pulp represents an inherent drawback in terms of preserving its vitality, attempts should be made to avoid such exposure by observing the principles of indirect capping. Then place the final filling. The same approach as for pulpitis prophylaxis is recommended for so-called “traumatic pulpitis”.

Important note
Suppression of the inflammatory mechanism by the glucocorticoid is inherently associated with a temporary reduction in the connective tissue activity of the pulp. If the pulp is exposed, care should therefore be taken to ensure that Ledermix Paste, a water-soluble preparation, does not remain on the dental pulp for too long (see under A above). If the water-soluble preparation is left in place unchecked or if the temporary filling is not hermetically sealed, there is a danger of pulp necrosis or the development of chromic pulpitis.

C: Cases of periodontitis
Both for primary acute periodontitis secondary to total purulent pulpitis and for acute episodes of chronic periodontitis, prepare the canal as far as the apex during the first session (mechanical and chemical preparation: Na hypochlorite, H_2O_2), dry and fill with Ledermix Paste, using a spiral plugger (lentulo). In the second session (approximately 1 week later), flush Ledermix Paste out of the canal (H_2O_2) and complete the gangrene treatment in accordance with one of the recognised methods. If there are signs of periodontic irritation (especially after the canal has been widened), during the course of root canal treatment, insert Ledermix Paste into the cleaned canal with a rotating motion and leave in place for about 1 week. In the next session, remove Ledermix Paste from the canal and, after an inert temporary filling, complete the root treatment.

4.3 Contraindications
- Hypersensitivity to the active substances, sodium sulphite or to any of the other excipients listed in section 6.1,
- Hypersensitivity to other glucocorticoids or tetracyclines,
- Purulent pulpitis,
- Root canal treatment of milk teeth.

4.4 Special warnings and precautions for use
Sodium sulphite may induce severe allergies and bronchial seizures (bronchospasms) in rare cases.

Important note: The glucocorticoid component of water-soluble Ledermix Paste is released throughout the entire period of application. Due to the antiproliferative effect of all glucocorticoids, the insert must not be left on the open pulp for prolonged periods (e.g. 2-3 days), so as to avoid potential pulp necrosis; the possibility that chronic pulpitis may develop should also be taken into account.

Paediatric population

Insufficient data are available for use in children (aged 3 years and older).

For safety reasons, its use in this patient group should proceed only after a very careful benefit-risk assessment, as the known systemic effects of glucocorticoids and tetracyclines cannot theoretically be excluded with any certainty.

4.5 Interaction with other medicinal products and other forms of interaction
None known when used as directed.

4.6 Fertility, pregnancy and lactation
Pregnancy
Ledermix Paste should not be used during pregnancy. Use of triamcinolone, particularly in the first 5 months of pregnancy, should be withheld, as animal trials have revealed indications of teratogenic effects and there are no available data on the safety of use in humans during this period. In long-term use, intrauterine growth disturbances cannot be excluded. For foetuses, there is a danger of adrenal cortex atrophy with treatment at the end of pregnancy.

Due to the antianabolic effect and teratogenic effects – including deposition in bones and teeth – demeclocycline should preferably not be used during pregnancy and breast-feeding.

Breast-feeding
Glucocorticoids are excreted in human milk. Breast-feeding should be discontinued if treatment with higher doses or long-term therapy is required. Demeclocycline penetrates the placenta barrier and is excreted in human milk. Due to the antianabolic effect and teratogenic effects – including deposition in bones and teeth – demeclocycline should preferably not be used during breast-feeding.

Fertility
No data are available on the effect of Ledermix Paste on fertility.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
The following frequency statements are used for evaluating adverse reactions:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Immune system disorders:
In very rare cases, allergic reactions including anaphylactic shock may occur. There is possibility of cross-allergies with other tetracyclines.

Sodium sulphite may induce severe allergies and bronchial seizures (bronchospasms) in rare cases.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose
No cases of overdose have been reported. Overdoses are not to be expected due to the method of application and very low absorption rate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Fixed combination of antibiotic and corticosteroid
ATC code: A01AB13 and A01AC01 "Stomatological preparations/Antiinfectives and antiseptics for local oral treatment/tetracylines" (A01AB13) and "Stomatological preparations/Corticosteroids for local oral treatment/triamcinolone" (A01AC01).
As active substances, Ledermix Paste contains triamcinolone acetonide (a powerful anti-inflammatory glucocorticoid) and demeclocycline (a broad-spectrum antibiotic). Clinical effect: Rapid pain relief for acute inflammatory conditions of the pulp and periodontium.

Demeclocycline is a broad-spectrum antibiotic of the tetracycline series and has bacteriostatic activity against tetracycline-sensitive Gram-positive and Gram-negative pathogens, as well as against *Chlamydia* spp., *Mycoplasma* spp., spirochaetes and *Rickettsia* spp. This includes both extracellular and intracellular pathogens. The mechanism of action is based on inhibition of bacterial ribosomal protein synthesis.
Triamcinolone acetonide is a fluorinated glucocorticoid with marked anti-allergic, anti-inflammatory and membrane-stabilising properties. Compared with cortisol, triamcinolone acetonide shows 160-fold greater glucocorticoid activity with practically non-existent mineralocorticoid activity. In topical cutaneous use, the following glucocorticoid effects on dermal cell systems have been described: inhibition of epidermis cell proliferation, reduced collagen synthesis, inhibited lymphocyte and granulocyte migration and proliferation, respectively, stabilisation of mast cell membranes, vasoconstriction of cutaneous vessels, inhibited pigment formation in melanocytes, inhibition of adipose cell proliferation.

5.2 Pharmacokinetic properties
In *in vitro* studies on extracted teeth with radiolabelled tetracyclines versus triamcinolone acetonide, both substances diffused in small quantities through root and crown dentine, depending on the number of dentinal tubules. Both substances were released in minimal concentrations (in the nMol range) over a period of days to weeks.

5.3 Preclinical safety data
Toxicological properties
Demeclocycline: Long-term studies with demeclocycline on animals showed minor toxic effects on haematology, blood chemistry and organ histopathology. Teratogenic effects have been found in animal experiments and also in humans. There are no indications of mutagenic or carcinogenic effects.
Triamcinolone acetonide:
Chronic toxicity studies were conducted on rats, dogs and monkeys. Blood dyscrasias, interference with the electrolyte balance, infections and liver changes were recorded depending on the dose, duration of treatment and method of administration, as well as some fatal outcomes. The observed shrinkage of the adrenal cortex and lymphatic tissue is directly associated with the glucocorticoid effect. In rats and dogs, an effect on clotting factors was observed in addition to the above-mentioned phenomena, as well as a reduction in glycogen levels in the liver, heart and skeletal muscle. No studies to investigate mutagenic potential were conducted and no long-term animal studies are available with regards to tumorigenic potential. Study finding available for glucocorticoids reveal no indications of any clinically relevant genotoxic properties. The embryotoxic properties of triamcinolone have been studied in three rodent species (rat, mouse, hamster), in rabbits and in three non-human primate species (rhesus, baboon, capuchin). In the rodents and rabbits, cleft palates and intrauterine growth disturbances occurred, with teratogenic effects, e.g. in rats, triggered by doses within the human therapeutic range. In the ape species, disturbances in chondrocranium cartilage formation were observed, leading to cranial anomalies (encephalocele) and dysmorphic facial features. In addition, deformities of the thymus and intrauterine growth disturbances occurred. No experience is available on the safety of use in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water purified, Macrogol 400, Macrogol 3000, Zinc oxide, Silica colloidal anhydrous, Calcium chloride dihydrate, Trolamine, Sodium sulphite anhydrous, Sodium calcium edetate.

6.2 Incompatibilities
Not applicable

6.3 Shelf-life
The expiry date of the product is indicated on the packaging materials
Shelf life after first opening of the tube is 2 months

6.4 Special precautions for storage
Do not store above 25°C

6.5 Nature and contents of container
Aluminium tube with 5 g paste

6.6 Special precautions for disposal and other handling
To prevent Ledermix Paste from hardening at the tube opening, the tube tip must always be kept clean and the tube sealed well after use. Colour fluctuations of Ledermix Paste have no influence on the efficacy of the product.

7. MANUFACTURER
Riemser Pharma GmbH
An der Wiek 7
17493 Greifswald - Insel Riems
Germany

8. REGISTRATION HOLDER
Neopharm LTD
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Petach Tiqva, 49170
Israel

9. REGISTRATION NUMBER
132-72-21420

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