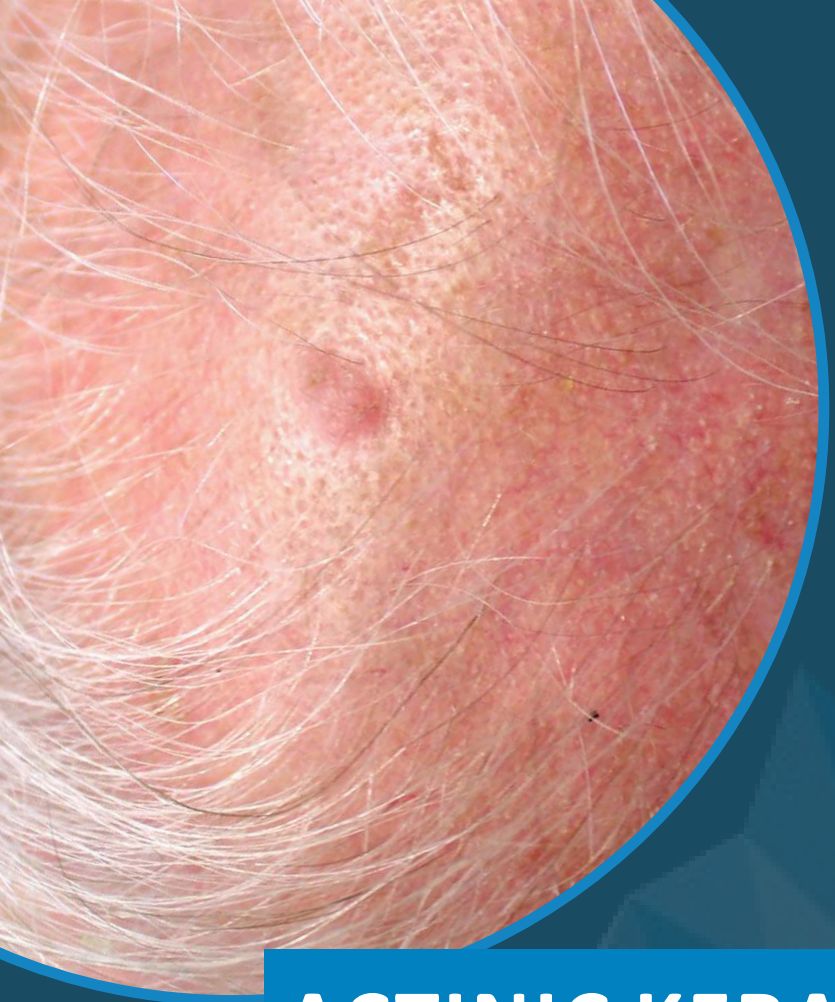

ACTINIC KERATOSIS

Treatment guidance

HYDROZID®

Actinic keratosis

Actinic keratosis, also called solar keratosis, is considered to be premalignant skin changes, primarily in the basal cell layer of the epidermis.

Among the causes for this development is long-term exposure to sun throughout life, and about 80% of all actinic keratoses are found in sun-damaged skin areas[1], with an increased prevalence in men[2] and persons with skin types I-II[3,4]. The prevalence for developing actinic keratoses increases from 10% at age 30 to 80% at age 70[2].
An additional risk factor is exposure to certain toxic substances such as arsenic and tar[5].

Certain patient groups are also at particularly high risk of developing actinic keratoses:

- HIV patients[2].
- HPV patients[5].
- Organ transplant patients receiving immunosuppressant therapy[2].
- Burn patients[2].
- Albinism patients[2].
- Xeroderma pigmentosa patients with DNA repair defect[2].

Actinic keratoses are often located on the head, scalp, ears and neck, on the back of your hand and the back of upper and lower extremities[3,6]. Actinic keratoses vary in thickness from atrophic to hypertrophic, and in size from 1 millimeter to several centimeters[6].

Actinic keratoses may occur individually, but are most often multifocal with an average of 8 actinic keratoses per patient[2]. In areas with chronic actinic sun damage and hyperkeratoses where at least 6 actinic keratoses occur in the same region of the body (a field), the clinical designation *field cancerization*[1,6] applies.

Actinic keratoses manifest as small, adherent pink or yellowish-brown scales. In clinical terms, actinic keratoses are divided into three severity grades[7]:

- **Grade 1**, increasing keratinisation (onset of hyperkeratinisation) where the skin feels rough on palpation and may feel like sandpaper. The changes are scarcely visible but can be seen in the light when viewed from the side. Pigmentation may occur[1].

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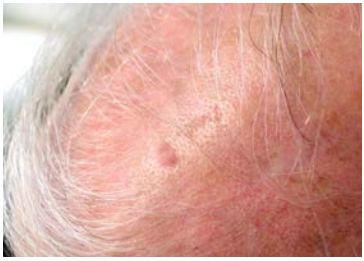
- **Grade 2**, moderately thick hyperkeratoses that are clearly visible and easily palpated[1].



- **Grade 3**, thick hyperkeratoses with a thickness of up to 1 cm. Infiltration may indicate malignant transformation with invasive growth[1].

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Early-stage actinic keratoses may itch slightly. When the lesions become hyperkeratotic, they may cause both functional and cosmetic impairment[1], and patients often seek treatment.

Until recently, it was assumed that grade III actinic keratoses were more dysplastic than grade II actinic keratoses. However, recent research indicates that both grades of actinic keratoses have the same level of dysplasia, which emphasises that all actinic keratoses should be treated, irrespective of their thickness[19].

If left untreated, actinic keratoses can penetrate the dermis, allowing the premalignant state to develop into non-melanoma skin cancer in the form of basal cell carcinoma (BCC) and particularly squamous cell carcinoma (SCC) of the skin[7]. The more actinic keratoses that can be registered on the same patient, the larger the

risk of developing SCC[2]. The risk of spreading is also increased if located near the bodily orifices[7].

However, timely treatment with cryosurgery can prevent this development.

Cryosurgery for treatment of actinic keratosis

Cryosurgery is among the most highly recommended treatment methods for actinic keratosis grades 1,2 and 3[1,3], based on several randomised clinical studies with comparable results, as well as meta-analyses[1].

In case of large areas with multiple, closely spaced actinic keratoses of varying severities, the recommended treatment is topical medical field treatments for both immunocompetent and immunosuppressed patients[1,7].

Immunocompetent patients

Cryosurgery is recommended for immunocompetent patients with:

- Multiple grade 1 actinic keratoses with fewer than 5 actinic keratoses within an anatomical area[1].
- Single-occurrence grade 1 actinic keratoses located on skin with visible actinic degeneration using *field cancerization*[1].
- Single-occurrence grade 2 and 3 actinic keratoses[1].

Immunocompetent patients with actinic keratoses need no follow-up after the completion of treatment but may be referred again in case of recurrence or development of new elements. For a small number of patients with severe actinic skin degeneration or multiple actinic keratoses, it may be relevant to schedule regular controls[1]. The therapist assesses the procedure for follow-ups or regular controls.

Patients receiving immunosuppressant therapy

Patients receiving immunosuppressant therapy are at a well-known and significantly increased risk of developing actinic keratoses and metastasis of spinocellular/planocellular carcinoma (SCC) in the skin[1].

For this reason, it is recommended to treat all types of actinic keratoses in patients receiving immunosuppressant therapy, irrespective of the severity or location of the actinic keratosis.

Treatment is repeated if the actinic keratosis recurs or in case of insufficient treatment response[1].

It is subsequently recommended that the patients are followed by dermatologists for life due to the immunosuppressant therapy[1]. The therapist assesses the procedure for follow-ups or regular controls

What is Hydrozid®

- Hydrozid® is an innovative CE-marked medical device that combines traditional cryosurgery with modern aerosol technology. Its patented, unique application system provides a simple, effective, treatment of actinic keratoses.

- Hydrozid® contains the gas norflurane and exposes the lesion to temperatures as low as -54°C to -58°C by means of a concentrated jet.[9,10] The consistent treatment temperature lasts for up to 4.5 minutes after treatment start and thus ensures a unique cold potential within cryosurgery. The necessary temperature for destroying benign cells using cryosurgery is between -20°C and -30°C, while for premalignant cells it is between -40°C and -50°C.[11,12] The varying reaction of skin cells to the low temperatures of cryosurgery enables the treatment of epidermal cells without damaging subcutaneous connective tissue, fibres or immune cells.[1]

- Hydrozid® treatment is based on the methods of freeze-thaw cycles and temperature control. Rather than continuous treatment exposure, studies have shown that repeated exposures to freezing followed by thawing (a freeze-thaw cycle) result in a more consistent and effective treatment.[13]
- These cycles afford the therapist more control of the treatment temperature and its effect on the treated area, which helps prevent overtreatment.[13] The low risk of side effects also allows for more frequent treatment of patients, which reduces the total treatment duration.

  All treatment with Hydrozid® should be adapted to the individual patient.


HYDR ZID®

Inform the patient before treatment

Provide the patient with the Hydrozid® patient instructions.

The patient instructions give relevant advice and information in brief about the treatment process.

The patient instructions are available free of charge at https://shop.hydrozid.eu or by email: info@hydrozid.com.

Treatment

Based on clinicians' experiences and patient experiences obtained from clinical studies, it can be concluded that anaesthesia during treatment of actinic keratoses is not necessary[8].

If you are in doubt about the diagnosis as a therapist, or suspicion arises about the disease progression during treatment, the patient should be referred for biopsy and assessment with a view to examination for planocellular carcinoma.

Application template

When treating actinic keratosis, use one of the accompanying application templates to protect the surrounding healthy tissue during treatment.

The application templates have 6 different holes of 3-10 mm in diameter. If the actinic keratosis is larger than 10 mm in diameter, treat it as described in the treatment section Treatment of actinic keratoses larger than 10 mm.

When treating actinic keratoses, it is advisable to apply treatment to the actual actinic keratosis and on 1 mm margin of surrounding healthy tissue.[14] You should therefore use the hole in the application template that covers the actinic keratosis and 1 mm margin of surrounding healthy tissue.

The treatment margins may become blurred during treatment as the formation of ice crystals covers the delimitation of the actinic keratosis and the surrounding healthy tissue. The application template can thus help focus on the limits of the actinic keratosis during treatment.

You can also use the application templates' size indications to compare the size of the actinic keratosis after each procedure to assess the effect of treatment.

The application templates can be used to treat multiple actinic keratosis on the same patient, after which they must be discarded.

Application template

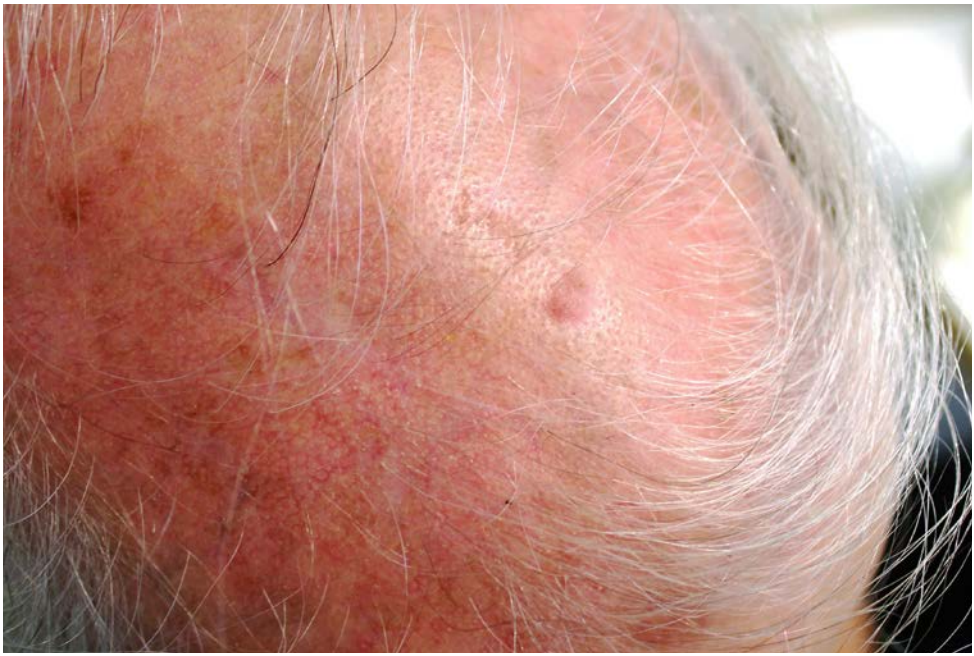
Treatment of one actinic keratosis, grades 1, 2 and 3

Actinic keratoses are most often multifocal, but may occur individually.

Treatment steps using Hydrozid®.
After unpacking – do not remove the tip of the application tube. It must remain in place during treatment.

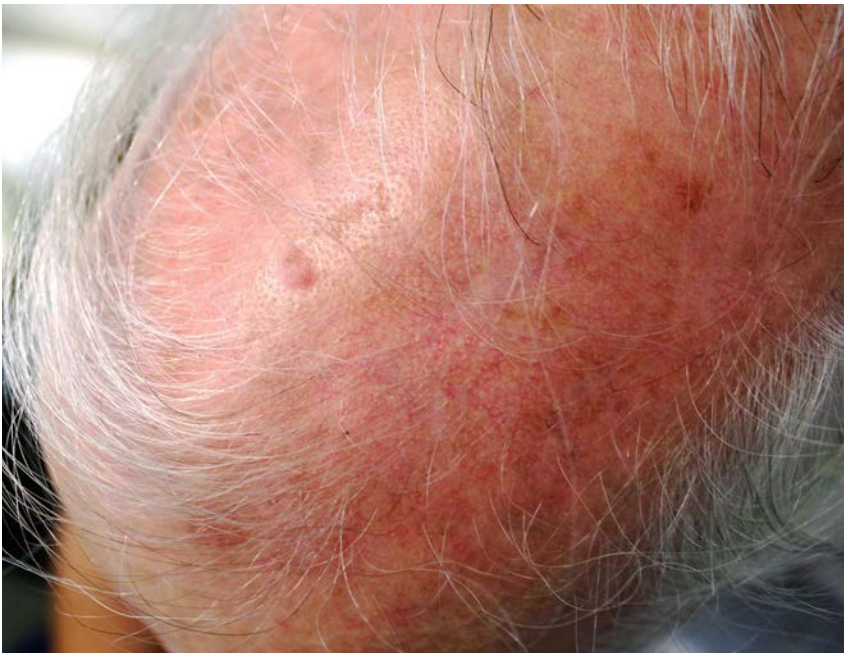
1. Release the locking mechanism under the activation arm, from left to right. The canister is now ready to use.

2. Hold the application template in place above the actinic keratosis with your non-dominant hand. Hold the Hydrozid® canister in your dominant hand as vertically as possible. Push lightly on the canister until you hear a hissing noise and the gas is released. If you push the canister too hard, the sound will be more like when dispensing a deodorant spray, which releases unnecessary amounts of gas with a risk of damaging surrounding healthy tissue. Also, this is not an economical use of the gas.



3. Spray at a distance of 2-3 centimetres from the actinic keratosis, for up to 5 seconds. A film of white ice crystals will now form in the treated area. Start counting when ice crystals start forming on the actinic keratosis[17].
After (up to) 30 seconds, the ice crystals are no longer white, indicating that the thawing period has ended. The first freeze-thaw cycle is now completed.

A distance of 2-3 centimetres corresponds to about 2 finger widths.



4. Then repeat another freeze-thaw cycle. The recommended number of freeze-thaw cycles is up to 2 cycles. The total treatment time is between 8-10 seconds.

The therapist assesses the patient and the treated area between each freeze-thaw cycle and must regard the treatment times as recommendations. Treatment for a longer period than recommended is associated with more frequent and more intense side effects.[15]

Treatment of 2-4 actinic keratoses, grades 1, 2 and 3

Actinic keratoses are most often multifocal with an average of 8 actinic keratoses per patient[2], close or disseminated, on sun-exposed skin[6]. In such cases, the treatment can be streamlined, as it is possible to treat 2-4 actinic keratoses within the same period of time as it takes to treat one (2 x 4 seconds - 2 x 5 seconds).

Treatment steps using Hydrozid®.
Prepare the canister and place the application template as described in treatment steps 1 and 2 in the treatment section *Treatment of one actinic keratosis, grades 1, 2 and 3.*

Next treatment steps:

1. Spray at a distance of 2-3 centimetres from the first actinic keratosis, for up to 5 seconds. While the ice crystals thaw and the thawing period passes, continue treating the second actinic keratosis.
2. Treat the second actinic keratosis using the same procedure. While the ice crystals thaw and the thawing period passes for actinic keratoses 1 and 2, continue treating the third actinic keratosis.
3. Treat the third actinic keratosis using the same procedure. While the ice crystals thaw and the thawing period passes for actinic keratoses 1, 2 and 3, continue treating the fourth actinic keratosis.
4. Finish by treating the fourth actinic keratosis for up to 5 seconds using the same procedure.

When the thawing period for the fourth actinic keratosis has passed, the first freeze-thaw cycle is complete. Now you can start a new freeze-thaw cycle on the first actinic keratosis, followed by the three others. Treat each actinic keratosis with 2 freeze-thaw cycles, of 4-5 seconds each, equating to up to 8-10 seconds total treatment of each actinic keratosis.

Treatment of actinic keratoses larger than 10 mm.

For actinic keratoses with a diameter larger than 10 mm, follow these treatment steps:

Treatment steps using Hydrozid®.
After unpacking – do not remove the tip of the application tube. It must remain in place during treatment.

1. Release the locking mechanism under the activation arm, from left to right. The canister is now ready to use.

2. Hold the canister in your dominant hand as vertically as possible. Push lightly on the canister until you hear a hissing noise and the gas is released. If you push the canister too hard, the sound will be more like when dispensing a deodorant spray, which releases unnecessary amounts of gas with a risk of damaging surrounding healthy tissue.

3. Spray at a distance of 2-3 centimetres from the centre of the actinic keratosis and continue by constant spraying in circular motions to the edge of the delimitation of the actinic keratosis. A film of white ice crystals will now form in the treated area. The treatment time of up to 5 seconds starts when ice crystals start forming on the actinic keratosis. The entire actinic keratosis must be covered by the ice crystals[17]

4. After (up to) 30 seconds, the ice crystals are no longer white, indicating that the thawing period has ended. The first freeze-thaw cycle is now completed.

5. Then repeat another freeze-thaw cycle. The recommended number of freeze-thaw cycles is up to 2 cycles. The total treatment time is between 8-10 seconds.

The therapist assesses the patient and the treated area between each freeze-thaw

cycle and must regard the treatment times as recommendations. Treatment for a longer period than recommended is associated with more frequent and more intense side effects.[15]

Side effects, healing process and treatment outcome

Cryosurgery therapy may cause a stinging or burning sensation during treatment.

The treated area may appear red, tender and swollen immediately after treatment.

Within 24 hours after the completion of treatment, inflammation develops in response to cell death.[16] This process contributes further to destroying the actinic keratosis and is a natural reaction in the inflammatory phase of the wound healing process.

Wounds and possibly blisters may subsequently occur in the treated area.[11] In such cases, the treated area must be protected with a plaster.

After treatment, the patient must keep the treated area clean by washing it daily with water and non-perfumed soap.

The patient should avoid exposing the treated area to sunlight for 10-14 days until the treated area is fully healed.

If repeated treatment is deemed necessary, a treatment interval of 1-2 weeks is advisable. The intensity and number of treatments depend on the patient's individual clinical response and is assessed by the therapist.

Precautions and contraindications

Hydrozid® must only be used by trained healthcare professionals.

Even though the effect of short freezing times as recommended in this material does not result in scarring,[11] Hydrozid® must be used with care to avoid damaging the dermis.

Exercise special caution when applying Hydrozid®:

- Near cutaneous nerves, tendons and nail beds[18].
- On persons with impaired arterial or venous circulation[18] (e.g. diabetes patients).
- In immunosuppressed patients.
- In persons with thin and/or sensitive skin (e.g. elderly with ageing skin, systemic scleroderma, persons treated with inhaled steroids for a prolonged period of time, etc.)[18]
- In persons with dark skin types. Even though the effect of short freezing times as recommended in this material rarely results in pigmentation changes in the treated area, hypopigmentation/hyperpigmentation may occur. This change is seen in persons with dark skin types in particular.[18]

Do not use Hydrozid®:

- On open skin lesions or eczematous skin to avoid subcutaneous emphysema[14].
- In patients with cryoglobulinemia, Raynaud's disease, cold urticaria, blood dyscrasias and Pyoderma gangrenosum[11].
- In case of uncertain diagnosis of the type of lesion (biopsy for skin carcinoma)[11].
- On healthy skin.

IF YOU HAVE ANY QUESTIONS OR, CONTRARY TO EXPECTATIONS, EXPERIENCE CHALLENGES WHEN USING HYDROZID®

Please contact Hydrozid® by email: info@hydrozid.eu

NOTES

Hydrozid® was developed by the Danish-owned family enterprise BIBAWO Medical A/S, Denmark, and is currently used in more than 20 countries around the world.

In Denmark, Hydrozid® is approved for the following therapeutic indications: acrochordon, actinic keratosis, cervical contact bleeding, condyloma acuminatum, gingival melanin hyperpigmentation, seborrheic keratosis, lentigo, molluscum contagiosum, verruca plana (flat warts), verruca plantaris (plantar warts), and verruca vulgaris (common warts).

Learn more about Hydrozid® on www.hydrozid.eu

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