A class IIa medical device intended for mild-to-moderate fungal nail infection

PRODUCT MONOGRAPH

Canespro®

Fungal Nail Treatment Set

- Removal of excessively infected parts of the nail in 2 to 3 weeks
- Clinically proven

From the makers of Canespro®

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Introduction to Bayer

Bayer is a Life Science company with a more than 150-year history and core competencies in the areas of health care and agriculture. With our innovative products, we are contributing to finding solutions to some of the major challenges of our time. The growing and increasingly aging world population requires improved medical care and an adequate supply of food. Bayer is improving people's quality of life by preventing, alleviating and treating diseases.

We develop new molecules, for use in innovative products and solutions to improve health. Our research and development activities are based on a profound understanding of the biochemical processes in living organisms.
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1. Onychomycosis: Background

Onychomycosis incidence

Dermatophytic onychomycosis, or tinea unguium, is relatively common across the Europe and North America, with prevalence estimated at 4.3% and risk of contracting infection increasing with age. Onychomycosis is more prevalent in men, and in individuals with psoriasis, immunosuppressive conditions such as diabetes and those with the HIV infection, and in patients who are taking immunosuppressive medications. Onychomycosis may occur in up to one-third of patients with diabetes, and it is a significant predictor of foot ulcers in this group.

2. Onychomycosis: Clinical features

Onychomycosis is a disorder affecting the structure of the nail. There are several clinical forms of onychomycosis. A classification of the different forms of onychomycosis has been informed by more recent understanding, of the underlying pathophysiology.

- Distal lateral subungual onychomycosis (DLSO) – This is the most common form of onychomycosis. In this form the fungus invades from the distal or lateral undersurface of the nail plate. Clinical features include hyperkeratosis, a range of discolouration of the nail including brown or black pigmentation, detachment of the nail from the nail bed, and streaking of the nail. Streaking can be found in other forms of onychomycosis, but is found most commonly in DLSO. DLSO is most commonly caused by dermatophytes.

- Superficial onychomycosis (SO) - The nail plate can be white or black and present with a wide range of discolouration. The nail surface is infected, whereas the rest of the nail plate, the nail bed, and the matrix remain unaltered. It can present as superficial patches or groove-like marks on the nail. The most common cause of SO is the dermatophyte Trichophyton mentagrophytes or rubrum.

- Endonyx onychomycosis (EO) - The nail plate is invaded through direct penetration of the fungal hyphae in the distal nail plate. It presents as length-wise splitting of the nail, along with discolouration in the nail plate however there is no nail bed invasion. In EO, the nail plate is most commonly invaded by Trichophyton soudanense or Trichophyton violaceum.

- Proximal subungual onychomycosis (PSO) - This classically originates from the proximal nail and nailfold, slowly extending distally. This form of onychomycosis is difficult to treat successfully. A wide range of fungi can cause PSO.

- Mixed pattern onychomycosis (MPO) – This classification of infection involves the occurrence of a combination of disorders seen in the same person at the same time. PSO and SO regularly occur together, as well as DLSO with SO.

- Totally dystrophic onychomycosis (TDO) - This presents at the end stage of different forms of nail plate invasion, and it is caused by different organisms. The nail is completely damaged and crumbles away, while the nailbed is thickened and ridged.
3. Onychomycosis: Clinical diagnosis

Onychomycosis is the most prevalent of the nail infections, accounting for approximately 50% of all abnormalities. Clinical diagnosis and treatment of fungal nail infections, will most often take place in primary care, although podiatrists and secondary care dermatologists will also treat fungal nail infections. An accurate diagnosis of fungal nail infection is important to ensure optimal therapeutic response.

Before treatment is given, microscopy and/or culture examination should be performed to confirm diagnosis. It should be noted that a direct microscopy and culture assessment may produce a false-negative result in up to 20% of cases, and culture assessment alone may result in a false-negative result of up to 40%. Results from traditional laboratory testing may take between 2 and 6 weeks to be returned.

Although considered a cosmetic condition in mild cases, onychomycosis can have a marked effect on quality of life. Untreated fungal nail disease, often spreads to other nails, and may spread to other areas of the body, potentially leading to fungal infections of the groin, hand and/or trunk, and can cause cellulitis in the elderly. Medically confirmed fungal nail disease should be treated in order to help improve quality of life, prevent impact of disease on daily activities, and reduce the chance for further infection.

4. Onychomycosis: Treatment pathway

There is no defined pathway for the management of onychomycosis, however the following pathway has been developed from review of literature recommendations.

Onychomycosis is associated with a high level of recurrence, with levels of recurrence reported between 40% and 70%. To aid prevention of relapse, fungal-free nails should be the treatment goal of therapy.
5. Interventions for onychomycosis

The following medical interventions are currently available for the treatment of fungal nail infection:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Method of administration</th>
<th>Duration of treatment</th>
<th>Active against</th>
</tr>
</thead>
</table>
| **Amorolfin hydrochloride 5% w/v Medicated Nail Lacquer** | Onychomycoses caused by dermatophytes, yeasts and moulds                    | The nail lacquer should be applied topically to the affected finger or toe nails once weekly. Twice weekly application may prove beneficial in some cases | 6 months (finger nails) 9-12 months (toenails) | Yeasts: Candida, Cryptococcus, Malassezia  
Dermatophytes: Trichophyton, Microsporum, Epidermophyton  
Moulds: Hendersonula, Alternaria, Scopulariopsis  
Dematiaceae: Cladosporium, Fonsecaea, Wangiella  
Dimorphic fungi: Coccidioides, Histoplasma, Sporothrix |
| **Tioconazole 283 mg/ml Nail Solution**          | Topical treatment of nail infections due to susceptible fungi and bacteria  | The solution should be applied topically to the affected nails and immediately surrounding skin every twelve hours using the applicator brush supplied | 6-12 months          | Commonly occurring dermatophyte and yeast-like fungal species |
| **Terbinafine hydrochloride Tablets 250mg**      | Fungal infections of the skin and nails                                     | One tablet once daily for varying durations depending on the severity of the infection | 6 weeks – 6 months   | Dermatophytes, moulds and certain dimorphic fungi   |
| **Itraconazole 200mg**                          | Onychomycosis caused by dermatophytes and/or yeasts.                       | One tablet once daily after food                                                          | 3 months             | Yeasts: Candida albicans, Candida parapsilosis, Cryptococcus neoformans, Malassezia spp  
Dermatophytes: Trichophyton spp, Epidermophyton floccosum, Microsporum spp, Trichosporon spp,  
Moulds: Aspergillus spp, Fonsecaea spp, Geotrichum spp, Pseudallescheria boydii  
Dematiaceae: Cladosporium spp  
Dimorphic fungi: Blastomyces dermatitidis, Coccidioides immitis, Histoplasma spp, Paracoccidioides brasiliensis, Penicillium marneffei, Sporothrix schenckii |
| **Griseofulvin BP 500 mg**                      | The treatment of fungal infections of the skin, scalp, hair or nails where topical therapy is considered inappropriate or has failed | One tablet once daily after food                                                          | 6-12 months          | Common dermatophytes                               |
| **Fluconazole 150mg**                           | Tinea unguium (onychomycosis) when other agents are not considered appropriate | One tablet once a week                                                                   | Treatment should be continued until infected nail is replaced. Estimated as 3-12 months depending on nail involvement | Common Candida species, C. glabrata, Cryptococcus neoformans, Cryptococcus gatti, Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum and Paracoccidioides brasiliensis |

Always refer to the product SmPC for specific details on individual products and their licenses.

For severe infections that do not respond to medical interventions, surgical or laser interventions may be considered.
6. Canespro fungal nail treatment set: Clinical features

Canespro fungal nail treatment set is a Class IIa medical device, intended for use for mild-to-moderate fungal nail infections. The Canespro fungal nail treatment set contains a 40% urea ointment. Urea is a keratinolytic agent which selectively softens the infected part of the nail leaving the non-infected parts of the nail intact.

Canespro treatment involves applying 40% urea ointment topically to the infected nail, every day for 2-3 weeks. Patients are required to follow the below process until the treatment is complete.

1. Soak infected nail in water for approximately 10 min and dry thoroughly
2. Apply a thin layer of the urea ointment on the infected area
3. Cover the affected nail with a plaster
4. After 24 hours, soak the infected nail in water again for approximately 10 min and dry thoroughly
5. With the use of the plastic tool included in the set, gently remove the softened part of the nail. It is essential that patients repeat the above process every day, until the infected part of the nail is removed.

7. Canespro fungal nail treatment set: Efficacy and safety

Canespro clinical data

A double-blind, randomized, multinational, multicenter, two-arm, placebo-controlled, parallel group study investigating efficacy of 4 weeks topical bifonazole* treatment for onychomycosis after nail ablation with 40% urea vs nail ablation with 40% urea followed by placebo.

- **Primary objective**
  Overall cure rate comprising clinical cure and mycological cure (both microscopy and culture negative) in the target nail assessed 2 weeks after end of treatment (EOT).

- **Secondary objectives**
  Secondary endpoints included clinical cure rate, mycological cure rate, mycological culture and microscopy at 2 weeks, 3 months and 6 months after EOT. Secondary endpoints for follow-up analysis at 3 and 6 months after EOT included the relapse rate (overall cure at visit 3, but positive clinical or mycological findings at visit 4 and/or visit 5). As an additional secondary endpoint the safety and tolerability of the study medication was assessed by collecting the number and type of AEs which occurred during the study.
Study design

Inclusion criteria:
- 18 years and over
- Positive clinical and mycological findings of onychomycosis
- Mild-to-moderate onychomycosis of finger nails or toenails (3 or less nails infected; \( \leq 50\% \) nail involvement and in the target nail between 20\% and 50\% involvement of the distal nail plate as an infected area)

Exclusion criteria:
- Patients with proximal subungual onychomycosis
- Patients with tinea pedis/manuum at baseline
- Patients with psoriasis (except affecting head/neck and torso only)
- Moderate-to-severe onychomycosis (more than 3 nails infected; >50\% nail involvement)
- Use of topical antifungal treatment for feet or hands within 4 weeks of screening
- Use of topical treatment for onychomycosis of feet or hands within 12 weeks of screening
- Use of systemic antifungal treatment within 6-9 months of screening

A total of 692 subjects were randomised to receive study medication, constituting the safety population.

A subject was evaluable for the primary endpoint if data on cure were both complete and assessable. The intention to treat population therefore comprised 595 subjects, 299 in the bifonazole group and 296 in the placebo group.

Nearly half of the subjects in both groups (48.5\% and 44.3\% for bifonazole and placebo respectively) had suffered from onychomycosis for >1 year. Similar proportions had short (<1 month: 32.4\% and 34.1\% respectively) and very long (> 2 years 32.4\% and 29.1\% respectively) duration of the condition.

*Bifonazole is not licenced for use for fungal nail infection in the UK.
Efficacy results

Nail ablation with 40% urea ointment took a mean of 18 days. The follow-on phase with bifonazole took place for 30 days.

At 2 weeks, 3 months and 6 months post EOT, samples were tested under microscopy and the investigator screened to identify potential clinical signs of onychomycosis reoccurrence. The absence of such signs were defined as the clinical cure for onychomycosis.

• Primary endpoint

At 2 weeks post EOT the overall cure rate was statistically superior in the bifonazole and urea 40% group vs. urea 40% alone (54.8% [n=164] vs. 42.2% [n=125] respectively; P = 0.0024) (Table 1).

• Secondary endpoint – efficacy

At 2 weeks post EOT, the clinical cure rate was similar in both treatment groups (86.6% [n=259] with urea 40% followed by bifonazole vs. 82.8% [n=245] with urea 40% alone) (p = 0.2109), however the mycological cure rate was significantly higher in the urea 40% followed by bifonazole group (64.5% [n=193]) than in the urea 40% alone group (49.0% [n=145]) (p = 0.0001).

At 3 months post EOT the overall cure rates were maintained with 50.7% [n=139] of subjects in the urea 40% followed by bifonazole group vs 40.9% [n=113] of subjects with urea 40% alone, showing overall cure (p = 0.0260). The clinical cure rate was similar in both treatment groups (74% [n=208,205] for both arms), whereas significantly more subjects maintained mycological cure with urea 40% followed by bifonazole (61.5% [n=174]) than with urea 40% alone (49.1% [n=144]) (p = 0.0033).

At 6 months after EOT, the overall cure rate was 33.6% [n=92] in the urea 40% followed by bifonazole group and 34.6% [n=98] in the urea 40% alone group (p = 0.8581). Clinical cure rate at 6 months post EOT was approximately 57% [n=158,162] in both groups. In addition, the mycological cure rate in the urea 40% followed by bifonazole group decreased to the level of the urea 40% alone group (bifonazole 52.1% [n=147] vs. placebo 48.1% [n=138]; p = 0.3568). See Table 1 for a detailed summary of the efficacy results.

<table>
<thead>
<tr>
<th>Analysis of parameter at</th>
<th>Treatment group</th>
<th>Comparison of treatments</th>
<th>Statistical test result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bifonazole N (%)¹</td>
<td>Placebo N (%)¹</td>
<td>Difference %</td>
</tr>
<tr>
<td>Overall cure rate³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 2 weeks</td>
<td>164/299 (54.8)</td>
<td>125/296 (42.2)</td>
<td>12.6</td>
</tr>
<tr>
<td>at 3 months</td>
<td>139/274 (50.7)</td>
<td>113/276 (40.9)</td>
<td>9.8</td>
</tr>
<tr>
<td>at 6 months</td>
<td>92/274 (33.6)</td>
<td>98/283 (34.6)</td>
<td>-1.1</td>
</tr>
<tr>
<td>Clinical cure rate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>at 2 weeks</td>
<td>259/299 (86.6)</td>
<td>245/296 (82.8)</td>
<td>3.9</td>
</tr>
<tr>
<td>at 3 months</td>
<td>208/282 (73.8)</td>
<td>205/278 (73.7)</td>
<td>0.0</td>
</tr>
<tr>
<td>at 6 months</td>
<td>158/278 (56.8)</td>
<td>162/285 (56.8)</td>
<td>0.0</td>
</tr>
<tr>
<td>Mycological cure rate⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 2 weeks</td>
<td>193/299 (64.5)</td>
<td>145/296 (49.0)</td>
<td>15.6</td>
</tr>
<tr>
<td>at 3 months</td>
<td>174/283 (61.5)</td>
<td>144/293 (49.1)</td>
<td>12.3</td>
</tr>
<tr>
<td>at 6 months</td>
<td>147/282 (52.1)</td>
<td>138/287 (48.1)</td>
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<td>Culture negative</td>
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<td></td>
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<tr>
<td>at 2 weeks</td>
<td>233/299 (77.9)</td>
<td>182/296 (61.5)</td>
<td>16.4</td>
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<tr>
<td>at 3 months</td>
<td>196/283 (69.3)</td>
<td>171/293 (58.4)</td>
<td>10.9</td>
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<tr>
<td>at 6 months</td>
<td>184/282 (65.2)</td>
<td>168/287 (58.5)</td>
<td>6.7</td>
</tr>
<tr>
<td>Microscopy negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 2 weeks</td>
<td>195/299 (65.2)</td>
<td>146/296 (49.3)</td>
<td>15.9</td>
</tr>
<tr>
<td>at 3 months</td>
<td>174/283 (61.5)</td>
<td>144/293 (49.1)</td>
<td>12.3</td>
</tr>
<tr>
<td>at 6 months</td>
<td>147/282 (52.1)</td>
<td>138/287 (48.1)</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Table 1: Efficacy results at 2 weeks, 3 months and 6 months after the end of treatment – descriptive statistics and statistical comparison of treatment groups (intent-to-treat population)¹⁶
Secondary endpoint - safety

In general, the incidence of adverse events was low for both treatments, although there was a higher incidence of adverse events in the urea 40% alone group vs. urea 40% followed by bifonazole.

Most frequently “skin and subcutaneous tissue disorders” and “infections and infestations” which were reported in both treatment groups. No other events showed any consistency.

During the urea treatment phase a total of 10 adverse events (2.9%) were documented in the bifonazole group vs 15 (4.1%) in the placebo group.

The incidence of AEs considered to be treatment related was very low and similar between the two groups. 0.6% was reported in the urea 40% followed by bifonazole group (n=347) vs. 0.9% in the urea 40% alone group during nail ablation (n=345), and 0.3% vs. 0.9%, respectively, during randomisation (n=692).

The respective AEs (skin irritation, erythema and inflammation in the urea 40% followed by bifonazole group; contact dermatitis, erythema, paronychia, exfoliative rash, peripheral oedema and dysaesthesia in the urea 40% alone group) were mostly reported of mild intensity.

Six subjects terminated the study early due to adverse events. Except for one case of assumed contact dermatitis in the urea 40% alone group, none of these were deemed to be treatment related.

Clinical data summary

- Non-surgical nail ablation offers a benefit in improving overall cure in topical onychomycosis therapy
- Chemical avulsion with urea should be regarded as an important option for topical treatment of onychomycosis
- Urea 40% is an effective topical treatment for fungal nail infection, with mean time to cure of 18 days, the follow-on phase with bifonazole took place for 30 days
- Follow-up with an antifungal treatment may increase overall cure rates, however this is not sustained in the longer-term

8. Canespro fungal nail treatment set: Availability and pricing

Canespro fungal nail treatment set was made available for over the counter purchase in 2013. To date, over 236,000 packs have been sold over the counter in the UK.

Canespro is priced at £18.74 per pack.

One pack of Canespro contains a 10g tube of 40% urea ointment, 22 single-use plasters and one plastic tool. One pack of Canespro is sufficient for two fingernails, two small toenails or one big toenail.

Treatment with Canespro should take between 2 and 3 weeks, making it the fastest acting fungal nail treatment currently available on prescription.

A demonstration video on the use of Canespro is available at: https://www.canesten.co.uk/en/derm/products/canespro-fungal-nail-treatment-set/?back_page_id=106

9. Further information

For further information, please contact the medical information department at Bayer PLC.
10. References

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13. Itraconazole SmPC. Available at: https://www.medicines.org.uk/emc/medicine/7395. Last accessed: March 2017
15. Fluconazole SmPC. Available at: https://www.medicines.org.uk/emc/medicine/25882. Last accessed: March 2017

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