

Novexatin[®]

A Novel Topical Agent for Onychomycosis

Novexatin,[®] a topical product developed by NovaBiotics Ltd., that contains a novel cationic peptide antifungal, has shown significant promise as a treatment for fungal infections of the toenail (onychomycosis) in preclinical and clinical testing, including Phase 1 and Phase 2a clinical trials. In the latter double-blinded, placebo-controlled trial, independent podiatrist analysis assessed the treatment as being 80% clinically effective against mild-to-moderate onychomycosis. This is a significantly higher rate of effectiveness than currently available topical treatments for onychomycosis in the United States, Europe, and other territories globally. Novexatin[®] moreover avoids potential safety issues that are associated with the use of orally administered systemic antifungal agents (see “About Novexatin[®]”).



Novexatin

Evaluation by Key Opinion Leaders

To help put the benefits and market potential of Novexatin® into context, NovaBiotics interviewed key opinion leaders in podiatry and dermatology who reviewed product research findings to date; podiatrists and dermatologists are expected to be the main prescribers of the product after regulatory review and approval (see “Dermatologists and Podiatrists Interviewed”).

Dermatologists and Podiatrists Interviewed

- Boni E. Elewski, MD, vice-chair for Clinical Affairs and professor of Dermatology, University of Alabama School of Medicine
- C. Ralph Daniel III, MD, dermatologist in private practice in Jackson, Mississippi
- Roderick J. Hay, MD, chairman, International Foundation for Dermatology, London, United Kingdom
- Warren S. Joseph, DPM, podiatric attending at Roxborough Memorial Hospital in Philadelphia, and a consultant in the treatment of lower extremity infectious disease
- Richard A. Pollak, DPM, MS, podiatrist in private practice in San Antonio, Texas
- Michael J. Trepal, DPM, podiatrist at the Foot Center of New York, an affiliate of New York College of Podiatric Medicine
- Aditya K. Gupta, MD, PhD, MBA, director of Clinical Research, Mediprobe Research, London, Ontario, Canada; and professor of Dermatology, Sunnybrook Health Sciences Centre and University of Toronto

Need for Effective Topical Onychomycosis Treatment

“Fungal toenails are a big problem, and the available treatments are not voluminous,” says Michael J. Trepal, DPM, a podiatrist at the Foot Center of New York, an affiliate of New York College of Podiatric Medicine. Toenail infections create not only cosmetic concerns, but also a thick, infected nail that rubs against the inside of a shoe or digs into the nail bed can cause pain as well, he says. For persons with diabetic neuropathy, he adds, such issues can even threaten entire limbs; unable to feel the pain from a break in the skin, these persons might not be aware of a cut until an infection develops.

“There is absolutely a need for a more effective, novel, fast-acting topical product for onychomycosis,” agrees Boni E. Elewski, MD, vice chair for Clinical Affairs and professor of Dermatology, University of Alabama School of Medicine.

Richard A. Pollak, DPM, MS, a podiatrist in private practice in San Antonio, Texas, notes that even modest improvement would be welcomed: “I don’t believe patients are expecting a complete cure. If a product was available that provided substantial improvement 25% or 30% of the time, that product would succeed.”

Aditya K. Gupta, MD, PhD, MBA, agrees: “We certainly do need a topical agent for onychomycosis. The oral agents have limitations, and existing topical agents have even more limitations. So there is a desire for a topical treatment that would be effective in the treatment of onychomycosis.” Dr. Gupta is professor

of Dermatology, Sunnybrook Health Sciences Centre and the University of Toronto and director of Clinical Research, Mediprobe Research, London, Ontario, Canada.

Dr. Elewski adds that a new topical product need not even be especially fast-acting or novel—it just needs to work better than Penlac® (ciclopirox, Sanofi-Aventis), the only topical prescription product currently approved by the Food and Drug Administration (FDA) for onychomycosis. She notes that in clinical trials, topical application of ciclopirox achieved cure rates of only 5.5% and 8% a year after treatment concluded.¹

Moreover, patients often must use topical ciclopirox daily for longer than a year, says Warren S. Joseph, DPM, a podiatric attending at Roxborough Memorial Hospital in Philadelphia. He says, however, that the product is sticky when applied. “Patients can end up with ‘black hairy toe syndrome’ when they remove their socks in the evening, and some sock fibers stick to where the Penlac® had been applied.”

“Patients generally prefer topical agents over oral ones because they perceive topical treatments to be safer.”

– Boni E. Elewski, MD

Even still, “Patients generally prefer topical agents over oral ones because they perceive topical treatments to be safer,” says Dr. Elewski, and with some validity. “We treat nearly all other fungal infections topically. Because most people who have onychomycosis are older and

may be on other medications, topical treatment is the way to go.”

As for systemic treatments, “There’s no question that oral terbinafine is effective for onychomycosis,” says Dr. Joseph. In pivotal clinical trials for Lamisil® (terbinafine, Novartis), one year after treatment (using doses specified in the product label), complete cure was achieved in 38% of patients.² He notes that the FDA’s cure criteria for this study were extremely stringent. Dr. Joseph estimates that in actual practice, 70% to 80% of patients who use oral terbinafine get better.

Moreover, Drs. Elewski and Joseph note that oral terbinafine is now available generically. Accordingly, with managed care formularies favoring the generic and little chance for a return on a manufacturer’s financial investment, Dr. Joseph sees little incentive for development of new oral antifungal agents. “Many companies that were working in this field have pulled out,” he observes.

Practitioners and patients, however, have concerns about using oral terbinafine because it has been associated with problems, including liver toxicity. “All the clinical trials have shown liver toxicity to be exceedingly rare,” says Dr. Joseph. This information is widely accessible via the Internet, he notes, “And there are enough internists and family doctors who are concerned about the possibility of liver toxicity to avoid prescribing terbinafine.”

“Terbinafine is a pretty safe drug and has been available for a long time,” says Dr. Elewski. Still, she notes, it can cause rashes and loss of the ability to taste foods.

“...99% of patients will choose to start with a topical treatment.”

– *Boni E. Elewski, MD*

Just the possibility of these adverse effects scares patients away from oral terbinafine, or to hesitate before taking it, or worry while taking it, she says. Once physicians inform patients of these possible adverse effects, 99% of patients will choose to start with a topical treatment. “If it doesn’t work,” she says, “then they’ll consider the oral agent.”

Dr. Gupta says, “Oral terbinafine has stood the test of time and has been quite effective. But there is a limit, an envelope, in terms of clinical and mycological cure rates. So we are indeed looking for something that might even go beyond this.”

Dr. Gupta says, however, that oral terbinafine “can be associated with adverse events. There can be drug interactions. There are issues that prevent its use, for ex-

ample, in persons with lupus or other concomitant medical conditions. Terbinafine worsens lupus. There are certain patients in whom we cannot use the oral agent because they are using medications that might interact with terbinafine, although such drug interactions are uncommon. All these factors require a good knowledge of what terbinafine can and cannot do, and its potential adverse effects. For example, a person with elevated liver function test findings must be evaluated to see whether he or she can be started on oral terbinafine, or any of the other systemic agents, for that matter. Therefore, a good topical—one that’s effective—would certainly be very desirable.”

“In terms of efficacy of onychomycosis treatments, there is room for improvement, even with the oral treatments.”

– *Roderick J. Hay, MD*

Roderick J. Hay, MD, chairman of the International Foundation for Dermatology,

About Novexatin®

Novexatin®, in clinical development by NovaBiotics Ltd., is a topical brush-on treatment for onychomycosis. It is the first treatment for fungal nail infections to address both the underlying cause by killing the fungi and to rapidly improve the nail’s appearance.

Novexatin® has been demonstrated to be safe and well-tolerated in two clinical studies and effective in resolving infection with just one month of daily application.

Onychomycosis affects an estimated 12% of the world’s population. Nail fungus is not merely a cosmetic condition; it also impacts the quality of life of those affected. Current treatments are either ineffective or associated with adverse effects. Thus, the need for Novexatin®, a safe, effective, and patient-friendly treatment for onychomycosis.

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London, United Kingdom, adds, “In terms of efficacy of onychomycosis treatments, there’s room for improvement, even with the oral treatments. For patients taking a drug orally every day for three or four months, to have a failure rate of 30% to 40% is not encouraging.” Indeed, he says, his patients in the United Kingdom, where he practices, often decline to treat their onychomycosis.

In the United States, oral itraconazole is also FDA-approved for onychomycosis. Dr. Elewski says, however, that virtually no one uses this drug because even as a generic, it costs around \$180 a month. “It also has several significant adverse effects,” and interacts with other medications.

Similar problems plague other systemic options including fluconazole, ketoconazole, and griseofulvin, says C. Ralph Daniel III, MD, a Jackson, Mississippi-based dermatologist in private practice. “They don’t work very well. They can have adverse effects, and they can interact with other medications,” he says. Several topical urea-based products that are available in concentrations from 20% to 50% also lack efficacy, he adds.

The field of onychomycosis treatment also has witnessed several high-profile development failures. “Terbinafine nail solution is the most obvious one,” says Dr. Joseph. The product looked promising in Phase 2 testing that was conducted outside of the United States, he explains. “But when Novartis did the Phase 3 trial in the United States, the drug’s efficacy was surprisingly low.” Seeing that the largest marketer of antifungal treatments could not succeed with a topical product,



he says, a dozen other companies halted development of their topical antifungal products.

“Patients in the United States have onychomycosis fatigue—they’ve been bombarded by advertisers and by their doctors with information about different treatments,” says Dr. Daniel. “Many patients who are serious about getting rid of their nail fungus have tried Lamisil® or other oral antifungals as well as various topicals. When these treatments don’t result in improvement, patients get frustrated. Many of them don’t go to the doctor anymore. Novexatin® should bring a lot of people out of the woodwork” to seek treatment for their onychomycosis once it gains FDA approval, he adds.

In the meantime, says Dr. Joseph, “Some over-the-counter (OTC) topicals are being marketed to the podiatrists for sale

to patients despite FDA regulations that manufacturers cannot market products for onychomycosis that are not approved specifically for this indication. Doctors like these products. They make \$20 or \$30 a bottle selling them in their offices.” Manufacturers of these products offer a money-back guarantee, Dr. Joseph adds. Whenever a patient is dissatisfied—which manufacturers claim rarely happens—the patient indeed gets a refund, and the doctor keeps whatever profit he originally made, he explains. Accordingly, says Dr. Joseph, “I believe that OTC products will be significant competition for Novexatin®, more so than any new prescription topical product.”

“I can’t tell you whether OTC topicals work or not,” says Dr. Trepal. He notes that none of the OTC products for onychomycosis have rigorous scientific data supporting their efficacy. “It’s all anecdotal.”

Entry of Laser Treatments

At the same time, Dr. Joseph says, “Laser devices are making a big push into the onychomycosis market.” Several devices have earned FDA 510(k) clearance, which he describes as “a very vague clearance for temporary improvement of the appearance of fungal toenails. Doctors are buying these lasers and charging patients \$500 to \$1200 per treatment session.” Dr. Trepal adds that results of laser treatments for onychomycosis that he has seen “haven’t quite lived up to the hype behind them.”

Dr. Gupta says, “Lasers are safe if used appropriately. In terms of efficacy, the jury is still out. The data that have been presented so far in the literature are not suggestive of efficacy. There may be some devices available that have increased efficacy but topicals have the advantage in that they can be used at home, unlike the devices,” which can only be used in a doctor’s office.

Dr. Joseph notes that one device has earned a general FDA 510(k) clearance for treating the skin, subcutaneous tissues, and nasal passages; its manufacturer also has applied for FDA clearance for treating onychomycosis. He says some patients favor the use of lasers for onychomycosis while others remain unimpressed. As more lasers gain FDA approval, he adds, “The cost may drop to \$500 to \$800 per treatment. These patients are willing to pay cash” because insurance does not cover these treatments.

Other companies are exploring alternatives, Dr. Joseph notes. Dr. Daniel says,

however, that it’s too early to determine if any of these technologies have clinical merit. “As far as I know, there’s nothing in development that would pose a serious competitive threat to Novexatin.”

For severely infected nails, procedures include debridement, which mechanically reduces the nail’s size or thickness, and surgical nail removal, possibly including matrixectomy, says Dr. Trepal. “Usually the nail that grows back is not appreciably better than one that was removed,” he notes.

Seeking the Ideal Treatment

“We need a topical agent with a cure rate of at least 8% to 38%,” says Dr. Elewski. Even with a complete cure rate of 20% in laboratory testing, she says, a new topical agent would be a blockbuster.

“We haven’t found the holy grail yet for onychomycosis,” says Dr. Joseph. “We don’t have one treatment that is safe, easy to use, and consistently effective.” Dr. Daniel adds that the ideal onychomycosis treatment also should cost relatively little and work quickly. “With fungal nail disease,” observes Dr. Trepal, “the changes are not dramatic, and they’re certainly slow. So patients get somewhat discouraged” with existing treatments.

Among existing agents, says Dr. Gupta, “Terbinafine is probably the most widely used, and rightly so. It’s got some efficacy, and it’s the best we have. The data show that it has a 38% to 39% complete cure rate and a mycological cure rate of about 70%. And the cost has certainly come down with generic availability in the United States. The cost is no longer an

issue. But the adverse event profile can be an issue. Therefore, it requires careful patient selection, as well as risk-benefit assessment. Again, a topical that’s more effective than what’s out there would be very welcome.”

Regarding safety, all experts interviewed agree that as a topical product, Novexatin® is free of concerns of liver toxicity and drug interactions associated with oral antifungals. “It’s reasonably certain that you’re not going to run into safety issues with 28 days’ application,” adds Dr. Joseph. Dr. Trepal points out that systemic absorption of Novexatin® is highly unlikely because the treatment is only applied to a very small area—the infected nail itself.

“The key will be efficacy. None of the [currently marketed] topicals are effective in moderate-to-severe disease.”

– Michael J. Trepal, DPM

The fact that Novexatin® is not associated with liver toxicity or other sequelae of systemic absorption is clearly an advantage, says Dr. Trepal. In Phase 1 and 2a clinical trials of Novexatin®, notes Dr. Elewski, blood tests revealed no evidence of the drug in the serum, except for a few patients who had very small amounts. Dr. Daniel concludes that the safety profile for Novexatin® is excellent because research has shown no meaningful presence of this drug in the serum or plasma.

A new topical product for onychomycosis must not cause irritation or contact derma-

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titis, adds Dr. Elewski. In this regard, Novexatin® showed a very good safety profile in Phase 1 and 2a clinical trials, she says.

“The key will be efficacy. None of the topicals are effective in moderate-to-severe disease,” says Dr. Trepal. “There’s nothing on the market in that category.”

Regarding ease of use, the experts agree that the proposed once-daily 28-day treatment regimen for Novexatin® can provide a significant marketing advantage.

Safety issues aside, says Dr. Joseph, oral terbinafine is easy to use — patients take one pill daily for three months. Conversely, he says, oral itraconazole requires “pulsed” dosing: two pills daily for one week, then off for three weeks. “No one could ever remember that.” With topical ciclopirox, adds Dr. Joseph, “every seven days, patients have to use alcohol or nail polish remover to remove excess buildup from the nail, and have their nail debrided.” Formula 3® requires twice-daily application, which, he says, is not convenient.

Conversely, says Dr. Joseph, “Anyone can use something once daily for 28 days. That will play a major role in patient adherence and satisfaction. No one else has that in this market.” Other products require three to four months of use, if not more, he observes.

“If Novexatin® works in 28 days,” adds Dr. Elewski, “it would probably have 100% patient adherence, or close to it, and high patient satisfaction.” Dr. Daniel adds, “28 days trumps every other treatment. That would be a key for marketing.” If NovaBi-otics markets Novexatin® with a brush-on

applicator,” adds Dr. Elewski, “it will be easy to apply.”

Dr. Daniel notes that dermatologists can be somewhat reluctant to treat onychomycosis with existing therapy choices. “One of the problems is that it takes a lot of time to explain the condition and how it is treated.” Accordingly, Dr. Elewski notes that many dermatologists use physician extenders such as nurses to educate patients about onychomycosis. Dr. Daniel has his nurses provide patients with a list of frequently asked questions and answers before he sees them. “It cuts the time that it takes to treat a patient’s nail fungus by about two-thirds.”

Supporting the need for a more patient-friendly approach for dermatologist-prescribed onychomycosis treatments, Dr. Gupta adds, “It’s likely that a topical agent would only need to be applied to the nail plate, and perhaps a bit of the surrounding skin. So the amount of [patient] counseling would be minimal.”

Dr. Gupta agrees with Dr. Daniel in that for dermatologists, “There’s a reluctance to treat onychomycosis because we don’t have anything effective. Many of my patients are 80 years old and older. I do not treat them with oral Lamisil®. It’s just not worth it,” because of potential adverse effects. “Also, knowing that the cure rate is what it is, and that the relapse rate can be high, and that there can be a bunch of other problems, why be a martyr? If I could have a topical that I could just give to them, possibly monitoring them at a distance, that would be fabulous.”

“Writing prescriptions for Lamisil® is a pain in the neck,” says Dr. Pollak. He has

to explain to patients why they need the drug, its possible adverse effects, and have patients visit a separate facility to undergo a liver function test. “Then I have to wait for the results of the blood work. A staff member has to pull the chart when we get the blood results. If the results are normal, we have to call the patient’s pharmacy—and we may have to call the patient to get the pharmacy’s telephone number. Then we have to notify the patient that the liver test result is normal, and he or she can now pick up the prescription.” He also needs to see the patient one month later to make sure there are no adverse effects or drug interactions. “That’s a lot of steps and none are reimbursed by insurance.”

Some patients try to skip that one month follow-up visit and request a refill from the pharmacy on their own. “Then we have to respond to a fax from the pharmacy saying, ‘No, we’re not going to write the prescription. The patient has to come in.’” These inconveniences explain why most podiatrists have not embraced oral antifungals, says Dr. Pollak.

If Novexatin® is shown to work anywhere near as well as Lamisil®, Dr. Pollak envisions the following scenario: “The patient comes in for one visit. I write the prescription. My assistant explains how to use the product. The patient returns for a follow-up visit six months later. Prescriber payment is the same for significantly fewer steps.”

Managed Care Coverage

Getting coverage for Novexatin® could be difficult, he says, because insurers generally consider onychomycosis to be



a cosmetic condition. “Insurers consider onychomycosis a cosmetic condition for one reason—so they don’t have to pay for it,” Dr. Joseph maintains.

When oral terbinafine was a branded product that cost nearly \$1000 per course, he says that physicians had to “jump through hoops” to get it covered. Conversely, says Dr. Joseph, “As soon as Lamisil® went off patent and generic oral terbinafine became available, there was no problem getting the drug. The insurers will claim that they are trying to promote better medicine and prevent overuse of drugs, but they are just trying to eliminate things they have to pay for.”

Dr. Joseph says that dermatologists and podiatrists consider onychomycosis to be much more than a cosmetic condition, in large part because it can cause pain. In one study that used a validated quality-of-life scale, researchers found that 48% of subjects with onychomycosis experienced pain.³ “How can a condition that causes

pain in 48% of patients be merely cosmetic?” he asks. Some evidence also suggests that in compromised patient populations such as persons with diabetes, onychomycosis can lead to foot ulceration and secondary bacterial infections, he says.

Ultimately, Dr. Trepal says that whether insurers cover Novexatin® will depend largely on its cost. “If it’s a very expensive product, insurance companies are either going to want to require that prescribers obtain prior approval” or otherwise limit its use by requiring higher copayments and/or requiring patients to try less costly therapies first. “It’s not just the price level,” he adds, “but the volume that’s going to be considered.”

“If the product has a reasonable [safety and efficacy] profile and isn’t horrendously expensive, general practitioners in the United Kingdom would treat more cases of onychomycosis,” says Dr. Hay. Dermatologists are far less reluctant than primary care physicians to use such a

product, he explains. “By the time patients reach us, their infections are usually much more severe.”

“Novexatin® certainly warrants further study. There’s plenty of proof-of-concept to merit further clinical research.”

– C. Ralph Daniel III, MD

Evaluating the Data

“In the Phase 2a trial, Novexatin® was evaluated by independent podiatrists as providing 80% improvement for mild-to-moderate onychomycosis,” notes Dr. Joseph. “There was a 40% improvement when severely infected nails were included in the evaluation. After a single 28-day course of therapy, this is very promising. NovaBiotics certainly has enough to go on to continue investigating the drug in a larger Phase 3 study, which is more than I can say for a lot of topicals” whose data he has reviewed. The Novexatin® results are all the more impressive because independent podiatrists are more critical evaluators than patients, he adds.

Dr. Daniel agrees that based on results of preliminary *in vitro* and Phase 2a trials, “Novexatin® certainly warrants further study. There’s no question about that. It’s all preliminary research, with relatively small numbers, but there’s plenty of proof-of-concept here to merit further clinical research.”

Based on *ex vivo* testing and Phase 2a results, Dr. Elewski concludes: “Novexatin® has excellent potential. It appears to work

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pretty well in vitro. And it performed significantly better with the brush-on applicator used in the Phase 2a trial." Moreover, she says, "It looks safe. It doesn't cause irritation."

"The data suggest that Novexatin® is very safe."

– Aditya K. Gupta, MD, PhD, MBA

Dr. Gupta adds, "The data would suggest that Novexatin® is very safe. Looking at the safety report provided, the conclusion is that the administration of one drop of a 9.3% solution on a fungally infected foot over 28 days was very well tolerated by all 48 subjects. That's reassuring to both physicians and patients."

In addition, says Dr. Gupta, "There were seven adverse events possibly or probably related [to the study medication] in five subjects. In some cases, there was a mild redness or erythema. Most of the adverse events are short duration. That's a very low adverse event profile."

Dr. Daniel adds that he was impressed with the precautions that researchers took with women of childbearing potential in the Phase 2a trial. Specifically, the women were not administered Novexatin® in part 2 of this study until the study's first portion confirmed that topical administration of Novexatin® did not result in systemic exposure. Accordingly, he says, "NovaBiotics' studies were very well done."

For all the above reasons, Dr. Daniel says that the safety profile for Novexatin® should provide a powerful point of differentiation from its competitors.

The patient diaries used in the Phase 2a study will be important for marketing to consumers, he explains, while independent podiatrists' evaluations will help in marketing to podiatrists.

"I congratulate NovaBiotics for doing some very elegant bench science with Novexatin,®" adds Dr. Joseph. "The nail penetration model used in the *ex vivo* nail assays was fascinating." Researchers applied nail fungus to the bottom of full-thickness, uninfected human toenails, then painted the tops of the nails with Novexatin® in various concentrations for 28 days and showed that Novexatin® dramatically reduced the presence of live fungi. "I've never seen that kind of *ex vivo* model before," he states.

"I congratulate NovaBiotics for doing some very elegant bench science with Novexatin.®"

– Warren S. Joseph, DPM

Dr. Hay says that he is impressed by NovaBiotics' *in vitro* work (from *in vitro* antimicrobial efficacy document, Table 6.4.1) looking at fungicidal activity. "The researchers incubated *Trichophyton rubrum* with Novexatin,® then subcultured the organism and showed that it's dead. From my perspective, and I suspect those of other dermatologists, that probably is more important than the nail model."

Dr. Elewski says that as a result of *ex vivo* testing, "We know that Novexatin® penetrates full-thickness nails in 28 days. We must treat not only the nail, but also the skin under the nail. Is one month enough time to allow the drug to diffuse into the nail bed? If a topical drug penetrates the full-thickness nail plate, it should get into the nail bed where the fungus resides. This is important, and this is why I believe the drug is potentially effective."

As for prophylaxis, Dr. Joseph applauds NovaBiotics' attempt at proving



Novexatin® prevents fungal infections through basic science research.

Dr. Daniel says that research into the mode of action (MOA) for Novexatin® indicates that Novexatin® has a significant postantifungal effect, which is defined as the period after complete removal of an antibiotic during which there is no growth of the target organism. In this research, exposure to Novexatin® for four hours resulted in a steady decrease in colony-forming units (CFU) of *T. rubrum* for the first two days. With one dose tested, investigators found no CFU remaining after days three and four. “That should be emphasized in marketing the product,” suggests Dr. Daniel.

Dr. Joseph adds that the prophylactic market is “huge,” noting that many patients spend significant sums to rid themselves of onychomycosis.

“Persons who contract onychomycosis are susceptible because the condition is inherited in an autosomal dominant fashion with incomplete or variable penetrance,” says Dr. Daniel. Because the fungus can be present anywhere from shoes to swimming pools, “once you clear up that fungus, to decrease the chance of relapse and reinfection, you need a product like Novexatin.® At the very least, even if it proves not to be efficacious as a primary product, if the company can show that it decreases relapse and reinfection, it will be worth its weight in gold.”

To date, says Dr. Daniel, no products have proven successful in this regard. He adds, however, that recent studies have shown that use of topical amorolfine and ciclopirox can reduce reinfection rates.

Mycological Versus Clinical Cure

NovaBiotics claims that Novexatin® is the first therapy to address both the cause and symptoms of onychomycosis by killing the infection source and rapidly improving the nail appearance and condition.

“Killing the source of infection means killing the infection,” or achieving mycological cure. “Improving the nail appearance means clinical cure,” says Dr. Elewski.

“Novexatin® can rapidly improve the nail appearance by killing the infection.”

– *Aditya K. Gupta, MD, PhD, MBA*

“I agree,” says Dr. Gupta. “Certainly Novexatin® can rapidly improve the nail appearance by killing the infection. It would be good to have a product that is effective” on both levels.

He adds, “Onychomycosis can indeed be symptomatic. Some infected toenails are painful and can limit mobility. Therefore, it would be important to have an agent that can reduce the symptoms of onychomycosis. In terms of the cause, it would be beneficial to have an agent that’s effective against both dermatophytes and nondermatophytes.”

As a physician, says Dr. Gupta, “I’m interested in curing the fungus. At the same time, one of the benefits of curing the fungus is that there should be nail clearing as well, which is what the patient is

looking for. The patient really doesn’t care whether the fungus is killed. The patient is looking for a good-looking, normal-appearing nail. A physician is also interested in that, as well as eradicating the fungal infection.”

“Clinical cure is most important for dermatologists. Making patients happy is first and foremost.”

– *C. Ralph Daniel III, MD*

Dermatologists likely will consider mycological cure and improvement rates very important, says Dr. Joseph. “I look at mycological cure rates as good news and bad news. The good news is, you’re mycologically cured. The bad news is, your nail still may look awful.” Moreover, he says, it is nearly impossible to satisfy the FDA criteria for a mycological cure. Nevertheless, he says, “At least we can use mycological improvement to extrapolate a bit in these early studies. Theoretically, a negative culture result indicates the fungus is dead.” If that’s the case, “We should empirically hope that as the nail continues to grow out, it will no longer be infected.”

“Clinical cure is most important for dermatologists,” says Dr. Daniel. “Mycological improvement is also important, but you can make these data look a lot of different ways” depending on how the statistics are presented. Mycological cure rates also will be crucial for gaining FDA approval, he adds. “The most viable hyphae are at the most proximal part of the nail. And it’s often harder for medications to penetrate proximally, and harder to collect samples

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from the edges of the nail, which can result in false negative cultures.

For patients, says Dr. Daniel, “The most important thing is appearance.” Each year, he explains, the approach of spring drives women to his office who are very concerned about how their toes will look in sandals. As long as their toenails look better, Dr. Trepal says, “Patients don’t care if some fungus remains.”

“For clinicians,” adds Dr. Daniel, “making patients happy is first and foremost.” This requires addressing the infection’s cause, he says. The foot can act as a reservoir from which fungus can spread elsewhere on the body.⁴ This can happen in otherwise healthy patients, he says, but it’s particularly problematic for persons with diabetes, those prone to cellulitis, and those who for whatever reason are unable to trim their toenails regularly.

“It’s important to treat persons with diabetes who have onychomycosis,” says Dr. Daniel. “If fungus starts on the toenail and gets onto the foot, it can cause a break in the skin, which can allow *Staphylococcus* or *Streptococcus* to enter. Also, the toenails of persons with diabetes are thicker and harder to cut. Thick toenails can also make breaks in the skin.”

“I like the fact that clinical trials for Novexatin® did not exclude persons with diabetes.”

– Warren S. Joseph, DPM

“I like the fact that clinical trials for Novexatin® did not exclude persons with diabetes. Many other studies exclude dia-

betes patients, who are predisposed to onychomycosis” and might not respond as well to treatment as patients without diabetes do, says Dr. Joseph.

Resistance Profile

Dr. Joseph applauds NovaBiotics’ “very elegant studies on resistance development by passing organisms through subinhibitory concentrations. I found it interesting that there was some implied resistance to itraconazole and terbinafine that didn’t develop with the Novexatin® peptide.”

Dr. Daniel also says these are important preliminary findings; Dr. Pollak says he also finds the lack of development of resistance impressive.

Dr. Elewski adds, “I particularly like that Novexatin® appears to be very good against some of the hard-to-treat organisms, like *Scopulariopsis brevicaulis*. It also had good minimum inhibitory concentrations (MICs) against *T. rubrum*.”

Compared with competitors, says Dr. Trepal, “The broader the action, the better.” The *Trichophyton* family causes most toenail infections, while *Candida* tends to occur on top of the nail, he says. He adds, however, “I suspect that some of the failures we’ve seen from other topical agents may mean that they are not efficacious against non-*Trichophyton*.” Dr. Trepal says that the nondermatophyte market could be substantial.

Dr. Trepal says he is satisfied with the MICs reported, as long as MICs remain below toxic levels, because other studies showed no resistance developing to Novexatin®. “You want to use the lowest dosage with the highest efficacy,” he says.

Fungicidal Versus Fungistatic

“I like the idea of Novexatin® being fungicidal,” says Dr. Joseph. “Fungicidal means more than bactericidal. If a treatment is fungicidal, it means it can kill the organism, and it’s not going to come back.”

This might be what allows Novexatin® to succeed with a brief 28-day treatment cycle (and should be emphasized in drug marketing, if this proves to be the case), he says. “If a treatment is merely fungistatic,” notes Dr. Elewski, “the organism will be only stunned. Once the patient stops using the drug, the infection will come back.” Topical competitors to Novexatin® are fungistatic.

“A fungicidal agent theoretically will allow less chance of relapse,”

– Michael J. Trepal, DPM

“A fungicidal agent theoretically will allow less chance of relapse,” adds Dr. Trepal.

“While killing the fungus is better than inhibiting it, if a product works, it doesn’t make that much difference whether it’s fungicidal or fungistatic,” says Dr. Daniel. He says, however, that proving Novexatin® is fungicidal (as preliminary research has shown) will be important to scientists, perhaps including those at the FDA. “Fungicidal is a marketable term,” adds Dr. Elewski.

Dr. Daniel says that NovaBiotics’ MOA study points out that “Novexatin® increased resting levels of cytosolic calcium and decreased levels of calcium influx in cytoplasm following stimulus.” That’s

indicative of potential membrane permeability, he says.

Regarding the product's MOA, explains Dr. Trepal, "It's a peptide. It's a little bit different from existing treatments, but it lyses the fungus, killing it. It makes sense to me as a clinician."

Potential as First-line Therapy

Regarding the potential impact of Novexatin® on prescribing habits, Dr. Elewski says, "If this product were available and worked in a short time or even took several months, I believe it would be embraced by dermatologists and podiatrists alike."

"If Novexatin® works in a month," adds Dr. Elewski, "that's clearly an advantage" over existing treatments. If it's approved as such, she says, she'd be very likely to prescribe it, as a first-line agent.

"If NovaBiotics can come up with a product that had proven efficacy—maybe an FDA-approved complete cure rate of 30% to 40%—with a once-a-day, 28-day drug that will be covered by insurance, I'd be very likely to prescribe it as a first choice," says Dr. Joseph.

For similar reasons, Dr. Daniel says Novexatin® "very likely" would fit into his practice as a first-choice topical for onychomycosis. "If I had something that had a good chance of working, I'd always try a topical before a systemic medication," he says.

"My job as a treating physician is to help my patients get better," says Dr. Daniel. "If I can tell a patient, 'use Novexatin® for a

month and you'll get better, I'm very likely to prescribe it" as a first choice among topicals, which he prescribes for mild onychomycosis and for patients who reject or are not appropriate for oral treatment.

Dr. Gupta says, "I'll prescribe any drug that is a topical that's effective." If the efficacy of Novexatin® is anywhere close to that of oral terbinafine, he adds, "it would be a huge seller. Why wouldn't it be first-line?" Overall, he says, "We're looking for something that's safe, easy to use in terms of patient adherence and length/duration of use, and at a good price. A topical is not associated with the systemic side effects of the oral agents. As for devices, patients cannot buy a laser and set it up at home."

Dr. Pollak adds that if Novexatin® performs in Phase 3 trials as well as it has thus far, he'd be very likely to prescribe it. Dr. Pollak says he is perhaps unusual among podiatrists because he's somewhat biased toward oral Lamisil® because of the efficacy it has shown in clinical research and in his practice. "Lamisil® is my first choice unless Novexatin® proves to me otherwise." If the efficacy of Novexatin® is anywhere close to that of Lamisil®, says Dr. Pollak, it may become his first choice. "If it's as effective as we hope it is, I see no reason not to use it," unless a patient simply cannot reach his or her toenails to apply the topical.

As for the potential of Novexatin® as cotherapy, Dr. Trepal says he puts 25% to 30% of his patients with onychomycosis on oral therapy. "And if it's bad enough to prescribe oral therapy, I recommend that we also use an adjunctive topical," such as Novexatin®, once available. "Not everybody uses adjunctive therapy. But

I tell patients, we want to hit this with all the heavy artillery we've got." In such situations, Dr. Trepal adds, "I will generally keep a patient on oral therapy for three months. When they're finished with the oral therapy, I commonly will have them continue with the topical" as long as clinical symptoms dictate.

Conversely, Dr. Elewski says that if Novexatin® is more effective than topical ciclopirox, practitioners likely won't need to prescribe a second agent with Novexatin®. Still, she says, she can envision cases in which she might treat a patient with moderate onychomycosis with one month of oral terbinafine (rather than the typical three months) to "jumpstart" the patient's treatment, followed by Novexatin®, which would minimize the patient's exposure to possible terbinafine side effects.

In this regard, says Dr. Gupta, "Studies could be done showing that you could shorten the use of an oral therapy. There could be synergy between the two drugs. All in all, there's exciting potential if indeed you could show this."

About 25%—maybe even 33% to 50%—of patients with onychomycosis are more than 60 years old, says Dr. Gupta. "Once you get over the age of 40—and our epidemiological work has shown this—the frequency of onychomycosis really takes off. So the whole world could benefit from Novexatin®, especially in this day and age, when people live longer, and they want to look healthy and show their feet off—both women and men. If you've got an effective topical agent, people would line up for miles to get it."

Novexatin

Likewise, Dr. Hay says that because of the high failure rate of existing oral drugs for onychomycosis, “like many dermatologists, I increasingly use combination therapy. I tend to use it more often than not.” He says, however, that his practice may have more severe cases than the typical dermatologist in the United States because he only sees patients who have not improved after treatment by a general practitioner.

“Like many dermatologists, I increasingly use combination therapy. Novexatin® is attractive [as adjunctive treatment] because it will be totally different from other treatments.”

– Roderick J. Hay, MD

Either way, Dr. Hay says, that as adjunctive treatment, “Novexatin® is attractive because it will be totally different from other treatments. Therefore, there’s a much higher probability that it would be synergistic” with oral terbinafine or itraconazole. “Because it has a different mode of action, it’s less likely to be antagonistic.”

“The only issue we have with combination therapy is insurance coverage,” says Dr. Joseph. “But if patients can get \$4 [oral] terbinafine and use it with Novexatin®, it makes sense that treating the fungus from the inside-out and the outside-in will produce better, faster cure rates.” Similarly, Dr. Daniel says he likely would use Novexatin® in combination with an oral antifungal around 50% of the time to increase overall efficacy.

Marketing Strategy

Dr. Elewski recommends marketing Novexatin® to dermatologists and podiatrists, although its safety and ease of use also would appeal to internists and family practitioners.

NovaBiotics should market to each specialty separately, suggests Dr. Daniel. “Dermatologists generally don’t read podiatric literature. For some reason, they’d rather see nonpodiatric data. I believe dermatologists know nails better than anybody else. And there’s a very small subset of dermatologists who know them better than most dermatologists. If you can get them on board, it adds a lot of credence to your data and presentations.” He considers Dr. Elewski to be among this subset of dermatologists.

Dr. Joseph predicts that key prescription competition for Novexatin® likely will come from Anacor’s AN2690 topical solution. Anacor is now recruiting patients for its Phase 3 trials. “Let’s say Anacor gets its approval, but the drug is used once daily for 48 weeks [as is planned for the Phase 3 trials]. If Novexatin® has comparable efficacy with a 28-day treatment cycle, Novexatin® will dominate.” Several products are a couple of years ahead of Novexatin® in development. “But we don’t know if any of them will be approved,” he adds.

A Truly Novel Option

“There have been no new antifungal compounds introduced in dermatology in more than 20 years,” says Dr. Elewski. “It’s exciting to have a new, novel product. I would play that up” in marketing

the product, along with the safety, broad-spectrum activity, and short-treatment course associated with Novexatin.®

The novelty of Novexatin® most likely will provide a marketing advantage, Dr. Hay says. “People are always intrigued by something that’s different, provided it works.”

“Novexatin® appears safe and effective, and it’s easy to apply.”

– Richard A. Pollak, DPM, MS

Dr. Hay adds, “There have been quite a few drugs in development in the last five to six years. These include several versions of topical terbinafine, a new treatment pack using urea, AN2690 (Anacor), and possibly a topical form of itraconazole. There are also some oral candidates under assessment, such as pramiconazole, albaconazole, and prothioconazole. Dr. Hay notes that none of these candidates has reached the market despite lengthy periods of evaluation.

Dr. Pollak agrees that the novelty of Novexatin® will prove to be an asset. “Everyone’s looking for a novel product in this market. Novexatin® appears safe and effective, and it’s easy to apply.”

Conversely, Dr. Trepal says that novelty will not drive acceptance of Novexatin.® Rather, sound marketing and solid proof of its superiority, at least over other topical agents, will. “NovaBiotics has to get the attention of podiatrists and dermatologists and must make sure Novexatin® is on the formulary of the managed care plans.”

Dr. Daniel agrees that if proof-of-concept results for Novexatin® hold up in larger clinical trials, the product “absolutely” would meet an unmet need and dominate as a first-line drug of choice for onychomycosis. He says he has reviewed data on so many drug candidates that it would be easy for him to be pessimistic about a product. “But with Novexatin®, I don’t see any reason to be pessimistic. This has potential.”

What’s Next?

Going forward, Dr. Joseph says, “The company has some great bench science and promising, early clinical proof-of-concept research. What it needs now is a good-sized clinical trial to show that Novexatin® works.”

Dr. Daniel and Dr. Joseph also stress the need to use an appropriately heterogeneous patient population [in subsequent clinical studies], in terms of sex and race, than previous “competitor product” studies have used.

Dr. Gupta adds that rather than testing Novexatin® against Penlac®, the only topical that is approved at present by the FDA for onychomycosis, “the FDA requires a placebo. Mild-to-moderate dermatophyte toenail onychomycosis—that should be the simplest to treat, and the easiest to recruit.”

In addition, Dr. Elewski applauds the wisdom of first obtaining FDA approval for dermatophyte infections. “Then other indications will come through reports authored by practitioners. The company won’t need to do any other studies” regarding nondermatophytes or special populations. Drs. Trepal, Hay, and Pollak agree with this assessment. “Whether or not it has an FDA indication for severe disease,” says Dr. Trepal, “doctors are going to use it off-label if it works for this patient population.”

In a study Dr. Daniel coauthored, “We found that onychomycosis developed on the feet about seven to 10 years before it did so on the hands. It developed on the hand patients used to scratch the feet or touch the toenail.”⁵ Dr. Hay suggests that the important secondary indication to pursue is severe nail infections, competing with oral therapies. “It’s a reasonable target,” but it would require an expanded clinical study with many more patients and a much longer follow-up.

“Pediatric patients would be the most important secondary subset of patients,” says Dr. Elewski. NovaBiotics might want to study this group, because FDA pediatric approval provides a six-month patent extension in this market. If Novexatin® truly does not enter the plasma, adds Dr. Daniel, it likely will be safe for children, although children account for less than

0.5% of onychomycosis cases. Overall, says Dr. Daniel, “It might not be worth the risk to do the studies in children, but it would make Novexatin® unique if it had that indication.”

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NovaBiotics Ltd., based in Aberdeen, United Kingdom, is a leading clinical stage biotechnology company focused on the design and development of first-in-class anti-infective therapies for difficult to treat, poorly served infectious conditions. NovaBiotics has looked to nature as the template for engineering a novel class of antimicrobial peptide therapies. The company's rational drug design approach and unique patented peptide anti-infective technology has already been validated through successful clinical development of the company's lead compound, Novexatin[®], a topical (brush on) treatment for fungal nail infections. A robust and exciting pipeline of drug candidates are also being developed for conditions such as life threatening blood stream fungal infections (predominantly candidaemia) and cystic fibrosis. More information is available at: <http://www.novabiotics.co.uk>.