



Pexiganan

(Genaera Corporation MSI-78, formerly LOCILEX)

An antimicrobial topical cream -
active against multi-drug resistant bacteria
(MRSA, MDRAB)

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Overview

The Genaera Liquidating Trust (the “Trust”) seeks to divest or otherwise monetize all its rights to pexiganan, a drug candidate developed by Genaera Corporation, the Trust’s predecessor in interest. Pexiganan is a novel, small peptide anti-infective developed in a topical cream form for treatment of patients with mild diabetic foot infection.

Pexiganan represents a unique drug development opportunity:

- Higher than average probability of approval – one new phase 3 study required.
- Product launch reasonably achievable within three years after funding;
- Unmet need – no topical antimicrobial compounds are specifically approved for mild diabetic foot ulcers; local treatment avoids toxicities and exposures of systemic therapy;
- Ability to treat drug resistant pathogens;
- Favorable risk reward ratio -- total development funding required from start to launch is estimated to be in the \$5 million to \$7.5 million range; and
- Highly credible pharmaceutical executives with the right experience are available to properly develop the compound picking up from the progress made to date.

Clinical Status

Pexiganan is the subject of an open IND and a pending NDA for diabetic foot infection

1998 - 2006: In clinical trials conducted by Genaera, over 1000 human subjects were exposed to pexiganan without safety concerns, including 418 patients who received pexiganan in two Phase 3 clinical trials submitted in a New Drug Application to the U.S. Food and Drug Administration (FDA) in 1998. In the Phase 3 trials 835 patients were randomized to pexiganan cream 1% or oral ofloxacin. The FDA judged the primary clinical endpoint of one of the two Phase 3 trials to have been achieved. The other Phase 3 clinical trial, which did not meet its specified endpoint, provided strong supportive data indicative of the clinical benefit of pexiganan. Additionally, more than half of the FDA advisory committee felt the Phase 3 studies should have been placebo controlled even though significant thought leaders in the medical community at the time asserted that placebo use in infected diabetic foot ulcers was potentially unethical. Difficulties with Chemistry Manufacturing & Controls (CMC), principally water separation, and an FDA request for one additional controlled Phase 3 study precluded approval at that time. As described in “Licensing History” below, pexiganan was subject to an agreement with SmithKline Beecham until late 2006, during which time Genaera took no further steps to develop the compound.

Current: By 2007 the environment to complete clinical development of pexiganan had improved on a number of fronts and continues to improve:

- significant advances in peptide manufacturing;
- improved understanding of the treatment of diabetic foot infections;
- improved clinical study design and execution for anti-infective compounds – a placebo controlled study can be designed to be safe for patients and acceptable to physicians;
- greater clarity around regulatory requirements for anti-infectives e.g. a recent Zyvox study that lead to FDA approval validated Infectious Disease Society of America (IDSA) guidelines for mild, moderate and severe infections.



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Licensing History

On February 12, 1997, Genaera Corporation (then known as Magainin Pharmaceuticals, Inc.) entered into a Development Supply and Distribution Agreement with SmithKline Beecham Corporation (later GSK) that gave SmithKline exclusive rights to Pexiganan and an option to control and distribute another Magainin product of its choosing if Pexiganan were not approved.

In July 1999 Magainin received a not approvable letter from the FDA citing cGMP deficiencies in the manufacturing of the drug product. The FDA recommended conducting a single additional clinical trial for the NDA to be approvable in the US market and described steps required to correct CMC issues. In the meantime, SmithKline had other anti-infective products on the market and in its development pipeline. Magainin shifted scientific/clinical priorities for its very limited resources away from anti-infectives, changed its top management and changed its name to Genaera. The SmithKline Agreement had the effect of keeping Pexiganan “on the shelf” until November 27, 2006 when Genaera obtained a termination letter from GSK.

Genaera sold an option to license Pexiganan to MacroChem Corporation for \$250,000 in July 2007. MacroChem exercised the option in October 2007, subsequently paid \$1,000,000 to Genaera and assumed all costs related to clinical development, manufacturing and regulatory activities. The royalties and subsequent milestones in the license were redacted in SEC filings but may be disclosed under a confidentiality agreement.

During 2008, MacroChem Corporation defined a course of action to go forward with the FDA and began to address the CMC issues to the point of preparing small batch GMP material. Those efforts included generating interest in and taking advice from medical thought leaders, publishing the clinical trial results for the first time and evaluating the environment in which to run a final Phase 3 study in subjects with infected diabetic foot ulcers that could lead to FDA approval.

In July 2008 MacroChem agreed to be acquired by Access Pharmaceuticals in an acquisition principally motivated by MacroChem’s oncology assets, oncology being Access’ strategic focus. The transaction closed in Q1-2009. Citing limited resources Access ceased development of MacroChem’s dermatology products including pexiganan.

On October 20, 2009, the Trust notified Access Pharmaceuticals and MacroChem Corporation that the licensing agreement would terminate November 20, 2009 and that the program assets are to be returned to the Trust.

About Pexiganan

Pexiganan is a 22-amino acid linear peptide. It is formulated as a cream and has a novel mechanism of action based on its ability to disrupt the integrity of bacterial cell membranes. It has antimicrobial activity against Gram positive (methicillin resistant staphylococcus aureus (MRSA)) and Gram negative organisms that commonly infect skin and soft tissue. It has a low potential for induction of resistance and no cross-resistance with existing therapeutic antibiotics as a consequence of its mechanism of action.

Genaera Corporation scientific staff and clinical prepared a detailed overview of preclinical work includes the following description that remains both accurate and relevant to this day:



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“...the distinguishing characteristic of pexiganan is its ability to cause membrane disruption in a broad spectrum of microbes, including gram-negative and gram-positive aerobic bacteria, anaerobic bacteria and certain species of fungi. This distinction, combined with the fact that the peptide-cell interaction is not receptor mediated, suggests that pexiganan possesses characteristics that reduce the potential for microorganisms to develop resistance.

Preclinical studies failed to elicit resistance to pexiganan following repeated-passage studies of strains including *S. aureus*, *S. epidermidis*, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*. Additionally, efforts to induce resistance in strains of *E. coli* and *S. aureus* through use of chemical mutagens failed. In contrast to some antimicrobial drugs, no evidence has been reported documenting the transfer of a resistance phenotype through either plasmid or chromosomal genetic transfer for a magainin peptide or any closely related molecule.

There is no cross-resistance between pexiganan and commonly used antimicrobials including penicillins, cephalosporins, carbapenems, quinolones, macrolides, lincosamides, sulfonamides, nitromidazoles, polymyxin B and polymyxin E. Pexiganan is active against pathogens that are resistant to these antibiotics.”

Manufacturing

Pexiganan may be produced by a solid or solution phase processes. Pexiganan API is extremely stable. The main CMC deficiencies raised by the FDA in the context of Magainin’s NDA filing concerned formulation, principally water separation. Genaera scientists also developed an *Escherichia coli* based recombinant manufacturing process for efficient, high level expression of pexiganan that has been demonstrated and replicated at laboratory scale. Genaera Corporation has maintained the recombinant process as a trade secret.

Intellectual Property

Pexiganan is covered in the US by a composition of matter patent that will expire in August 2016, but which can be extended under Hatch Waxman until late 2019 at the earliest and potentially until August of 2021 at the latest. The patent is issued to Scripps Institute and held by the Trust pursuant to a fully paid up license.

Market Information

According to the Centers for Disease Control and Prevention (CDC), the estimated incidence of diabetes in the US exceeds 1.5 million new cases annually, with an overall prevalence of nearly 24 million people (2008), or more than 7% of the US population. It is estimated that as many as one in four persons with diabetes will develop a foot ulcer in their lifetime of which about 60% become infected. Diabetic foot ulcers generally result from the consequences of peripheral neuropathy. Peripheral vascular disease, increased biomechanical stress and acute trauma further increase the risk of foot ulcers. It typically takes several months for an ulcer to heal, and during this period there is a continual risk of foot infection. Infected foot ulcers can result in bone infection (osteomyelitis) or progressive gangrene. Diabetes is now the top cause of non-



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traumatic leg amputations in the developed world. Additionally, foot ulcers are now the most frequent cause of diabetes-related hospitalizations. The total annual cost of foot ulcer care in the US has been estimated to be as high as \$5 billion. Thus, diabetic foot infection is a major burden to patients resulting in long-term disabilities and continuing high demands on the healthcare system.

Remarkably, pexiganan may prove to be an especially timely product in spite of time lost. Currently, no topical antimicrobials are specifically approved for the treatment of diabetic foot infections. Concern as to treatment of antibiotic resistant pathogens has only grown over time. Moreover, the economics of treating mild diabetic foot infections with a topical antimicrobial favor pexiganan. Even an expensive topical for resistant pathogens at the “mild” stage should compare favorably to treating more advanced infections. Pfizer’s Zyvox was recently approved for diabetic foot infection. Zyvox, labeled for “certain serious bacterial infections that are often resistant to other antibiotics” can cost over \$2,000. Even so, in a study presented to the IDSA in 2005 total treatment costs using Zyvox were much lower than other antibiotics for serious infections. Pexiganan has the potential to be an initial therapy for resistant pathogens in mild diabetic infections and to augment systemic therapy in more serious infections.

Pexiganan sales potential is estimated to exceed \$100 million annually with some estimates over \$500 million. The Trust is commissioning a study of the market potential for pexiganan. [For initial discussions we assume a number closer to the \$100 million for the approved indication].

Other potential indications for which pexiganan may provide beneficial therapy include: MRSA - cutaneous and systemic methicillin-resistant Staphylococcus aureus; central venous catheter infections; Infections of prosthetic/skin interfaces and acne. Genaera received expert advice to the effect that a lower concentration level, <0.2% w/w, pexiganan has the potential to be included in over-the-counter (OTC) and/or cosmetic applications for the treatment of acne.

Additional Information

The Trust can provide detailed information from public sources and confidential records, including IND and NDA documents, FDA communications, a wide range of scientific and preclinical data and scientific journal articles including Phase 3 results published in the Clinical Infectious Diseases Journal on December 15, 2008. Interested parties should contact:

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