

# TRANSDERMAL DELIVERY:

SUCCESS THROUGH A DEEP UNDERSTANDING OF THE SKIN



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## “Transdermal delivery: success through a deep understanding of the skin”

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## CROSSING THE BARRIER: RF TRANSDERMAL DRUG DELIVERY

RF skin ablation is an established medical technique that has been commonly used for surgical procedures. TransPharma has modified and implemented the use of RF ablation and developed the RF-MicroChannel technology to create passages through the skin that allow a novel and unique approach for transdermal drug delivery. Dr Galit Levin, Vice-President of Pharmaceutical R&D and Judith Kornfeld, Vice-President of Business Development, both of TransPharma Medical Ltd, describe the current status of this approach.

Passive transdermal drug delivery has been in use for more than 20 years, and while it provided significant advantages over preceding technologies, it was successful only with a limited number of active molecules. In fact, very few drugs can passively diffuse across the skin barrier at therapeutically useful rates. To expand the limits of transdermal drug delivery, TransPharma Medical has applied and modified radio frequency (RF) cell

remain open for a relatively long time, up to 24 hours. This enables sustained-release drug delivery to maintain constant drug blood levels and improved compliance. In addition, with TransPharma's proprietary patch technology, a peak shape delivery, similar to that of subcutaneous injection, can also be obtained.

Electrodes are created by placing a closely spaced array of tiny electrodes against the skin. An alternating electrical current at a particular high (radio) frequency is then transferred through each of the microelectrodes, which forms microscopic passages in the stratum corneum

### RF-MICROCHANNELS ARE A UNIVERSAL SOLUTION THAT CAN EXPAND THE RANGE OF MOLECULES THAT CAN BE DELIVERED TRANSDERMALLY

and outer epidermis via a process called cell ablation. ablation technology to develop a unique method for painlessly, accurately and safely creating microchannels in the skin's surface to enable transdermal delivery of drugs that cannot be delivered using current technologies.

The technology provides the following advantages:

- RF-MicroChannels are created within milliseconds, with no resulting skin trauma or pain.
- RF-MicroChannels can be used to deliver a wide variety of molecules through the skin.
- The size and the density of the RF-MicroChannels are fully controlled and predictable, due to the feedback mechanism incorporated in the device. Consequently the delivery is fully controlled and may be altered to meet various delivery demands with high or low delivered doses.
- Delivery profiles: electrode formed in the skin

and outer epidermis via a process called cell ablation.

As shown in Figure 1, these RF-MicroChannels penetrate only the outer layers of skin, where there are no blood vessels or nerve endings, minimising any skin trauma or unpleasant sensations. The passages created can be used for either drug delivery or analyte extraction. The whole process is performed rapidly, taking only seconds to complete.

A typical RF-MicroChannel array uses hundreds of microelectrodes, creating hundreds of parallel MicroChannels through the skin in a few seconds, as shown in Figure 2. The drug delivery rate is determined by the size and number of channels created, which are in turn functions of the number and density of the activated electrodes and the electrical current passing through them.



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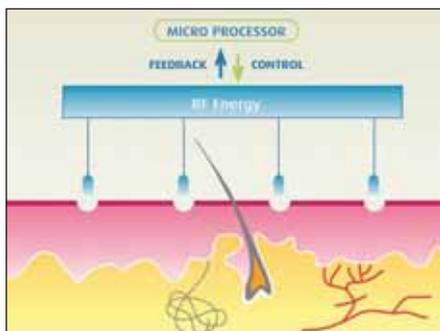


Figure 1: RF-MicroChannel formation

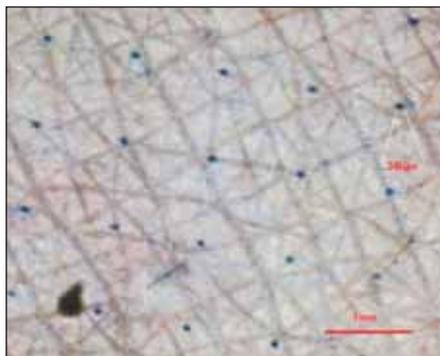


Figure 2: Stained RF-MicroChannels on human skin (50x magnification)

## THE VIADERM DRUG DELIVERY SYSTEM

TransPharma's RF-MicroChannel Technology is implemented in the ViaDerm drug delivery system. Intended for home use and designed for self administration by the patient, the ViaDerm system consists of a reusable battery-operated handheld electronic control unit, a disposable low-cost microelectrode array and a patch containing a drug. The reusable device, with disposable microelectrode array attached, creates the RF-MicroChannels. This prepares the site for application of a patch containing a drug (Figure 3). The drug is then passively diffused through the RF-MicroChannels into the inner skin layer and from there to the systemic circulation.

The ViaDerm device is available in three sizes (Figure 4), depending on the desired dose



Figure 3: Applying the ViaDerm system to the skin



Array Dimensions: 5.0 cm<sup>2</sup> 2.5 cm<sup>2</sup> 1.0 cm<sup>2</sup>

Figure 4: ViaDerm devices

of drug to be delivered. All three units are designed to enable easy application by the patient with minimal initial training.

## PATCH TECHNOLOGY FOR PROTEIN DELIVERY

Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. TransPharma uses its unique printed-patch technology for transdermal delivery of proteins thereby complementing its ViaDerm delivery technology (figure 5). Such printed patches contain accurate doses of proteins in a dry state. It is postulated that the highly water-soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-MicroChannels, forming a highly concentrated protein solution *in situ*.

The delivery of the dissolved molecules is then carried out, via the RF-MicroChannels, into the viable tissues of the skin, diffusing across a steep concentration gradient. This brings about a high delivery rate, as well as a peak blood profile of the drug resembling that of a subcutaneous injection. The protein patches do not contain any enhancers to facilitate the delivery process, thereby insuring an easier development process and regulatory pathway.

TransPharma has adapted a manufacturing dispensing technology, widely used in the

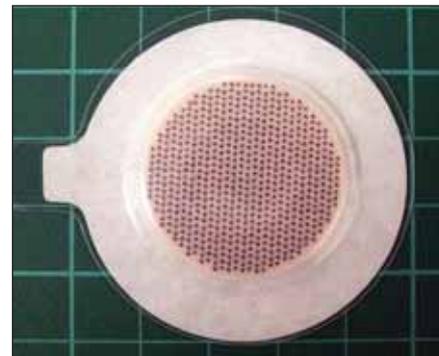


Figure 5: Printed patch

diagnostics industry, to successfully manufacture the printed patches. This manufacturing method enables complete and flexible control of drug load on the patch, control of patch size and shape, as well as high manufacturing yield with minimal protein losses. In addition, it was found that this manufacturing method fully retains the biological activity of the protein drug.

Printed patches were used in studies in which human growth hormone (hGH), insulin, and Teriparatide (PTH<sub>1-34</sub>) were delivered in animals (guinea-pigs and pigs) and humans.

## DRUG DELIVERY THROUGH THE MICROCHANNELS

### General principles

1) **Molecular size** – Currently there is no known limit to the size of drug molecules that can penetrate through the MicroChannels. The transdermal delivery of water soluble small-molecule drugs can be increased significantly by ViaDerm pre-treatment. In addition, macromolecules such as peptides and proteins can also be delivered systemically through the skin using this technology.

2) **Solubility in water** – The MicroChannels are filled with interstitial fluid. Therefore, water soluble molecules can be easily delivered through the MicroChannels into the inner skin layers and the systemic circulation. Water insoluble drugs can be delivered trans-

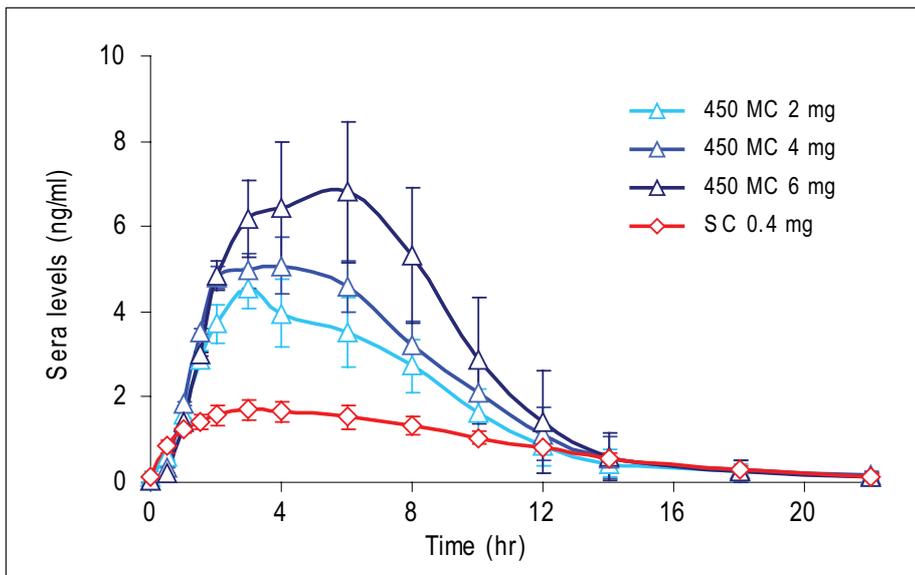


Figure 6: Clinical Study-hGH delivery through MicroChannels as compared with subcutaneous delivery (Crossover study, n=6 in each transdermal group, 4.9 cm<sup>2</sup> patch loaded with 2, 4, 6 mg hGH)

dermally using the ViaDerm system by increasing the water solubility using a suitable formulation.

**3) Concentration** – The delivery is based on a passive delivery through breached skin. As in any passive delivery, the rate of delivery depends on the concentration gradient. Increasing the drug concentration on the skin in the vicinity of the MicroChannels will result in a higher delivery rate.

**4) MicroChannel density** – By increasing the MicroChannel density (MCs/cm<sup>2</sup>) a higher amount of drug can be delivered. This may bring about a more efficient delivery process or enable the delivery of a higher one-time dose.

**5) Duration of delivery** – The duration in which enhanced drug delivery can be observed is up to 24 hours, after which the delivery rate will be similar to that through intact skin. Therefore, the maximal patch application time should be 24 hours.

**6) Drug dosage forms** – The most convenient dosage form to use in combination with the ViaDerm technology is a patch, which has a drug area size matching the size of the ViaDerm electrode array. However, simpler dosage forms such as gels or creams can also be used. It was shown that by applying semi-solid dosage forms on ViaDerm treated skin the delivery of drugs could be increased significantly compared with the intact skin.

| Drug  | Patch Dose (µg) | MC Density (MCs/cm <sup>2</sup> ) | Relative Delivered Dose (µg) | Relative Bioavailability (%) |
|---|-----------------|-----------------------------------|------------------------------|------------------------------|
| hGH (22K)D<br>Patch Size:<br>4.9(cm <sup>2</sup> )  | 4000            | 150                               | 200                          | <b>6.0</b>                   |
|   | 4000            | 300                               | 600                          | <b>14.6</b>                  |
|   | 2000            | 450                               | 700                          | <b>36.5</b>                  |
|   | 6000            | 450                               | 1100                         | <b>18.9</b>                  |
| hPTH (1-34)<br>Patch Size:<br>1.0(cm <sup>2</sup> ) | 90              | 150                               | 54                           | <b>59.5</b>                  |

Table 1: Summary of clinical trials

**7) Drug profile** – The result of transdermal delivery using the ViaDerm system can be a peak plasma profile or a constant blood level, depending on the type of patch technology used.

**8) Type of patches** – A reservoir patch, usually a water-based hydrogel, can be used to incorporate small or large molecules and apply them on the skin. A hydrogel patch maintains the skin in a hydrated state, and therefore enables drug delivery in a constant level for up to 24 hours. For proteins, the use of a printed patch is advisable. The resulting blood profile is in a peak shape that resembles that of an injection. The use of printed patches also results in a very efficient and cost-effective delivery

**9) Lack of reservoir in the skin** – One of the most disturbing issues regarding passive delivery is the accumulation of drug in the stratum corneum due to the affinity between hydrophobic drugs and this lipidic tissue. This reservoir continues to release active drug into the circulation long after the treatment is stopped, decreasing the accuracy of treatment. The ViaDerm technology delivers water soluble drugs that do not accumulate in the stratum corneum. Therefore the issue of reservoir formation does not arise.

## TRANSDERMAL DELIVERY OF LARGE-MOLECULE DRUG PRODUCTS

TransPharma's unique transdermal technology enables the systemic delivery of therapeutic doses of a wide range of drug molecules, including biologics, a rapidly growing market. In 2004, the drug delivery market was estimated at \$60 billion, with an annual growth rate of approximately ten percent, a significant portion of which is driven by biologics, which are currently available primarily by injection. TransPharma is capitalising on the market potential for biologics while simultaneously addressing its drug administration limitations. By offering a solution that provides increased efficacy, safety and compliance while avoiding the need for injection, TransPharma is addressing an unmet need in the biologics market.

TransPharma is building its product pipeline through proprietary product development and partnerships with leading pharmaceutical companies. In-house, we are developing a transdermal hPTH (1-34) drug-product, which will enable patients to manage their osteoporosis while eliminating the need for

painful daily injections. hPTH (1-34) is currently the only osteoporosis drug to possess anabolic properties. Over the next five years, the number of people suffering from osteoporosis is expected to reach 52 million, creating a \$10.4 billion market by 2011.

TransPharma recently completed initial Phase I clinical trials of hPTH (1-34) which yielded extremely promising results. hPTH (1-34) was delivered via TransPharma's proprietary ViaDerm-Micro system with extremely high bioavailability relative to the therapeutic dose (20 µg) of subcutaneous injection. Furthermore, the blood profile achieved was of a relatively sharp peak profile.

In addition, TransPharma has recently successfully completed initial clinical trials on human growth hormone (hGH), currently available by subcutaneous injection only. Example results obtained in one of these trials are shown in figure 6. This achievement marks the first development milestone in our collaborative drug-product development agreement with Teva Pharmaceutical Industries, which includes up to five molecules designated for joint development.

Table 1 shows that a low (i.e. 6%) or high

(up to 60%) relative bioavailability is attainable, depending on the ratio between the amounts of active material and MicroChannels. In order to get high bioavailability as well as high delivered dose, it is necessary to optimise several factors: patch size, dose of active pharmaceutical on the patch and MicroChannel density. The optimisation should also take into account the required daily dosage of each drug.

### FUTURE DIRECTIONS

TransPharma is focused on products for which our technology will provide clear benefits over existing therapies. Such benefits could include improving safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained release patch formulations, among others.

Other therapeutic fields hold considerable potential for product candidates whose ultimate therapeutic use can significantly benefit from our technology. For example, the ViaDerm system may be applied to the delivery of local medications for topical applications in the fields of dermatology and cosmetics. The ViaDerm system may also allow

enhanced immunisations, providing a non-painful, safe and effective alternative to current intramuscular or subcutaneous vaccination methods.

RF-MicroChannels are a universal solution that can expand the range of molecules that can be delivered transdermally and allow improved penetration and better dosage control. In the future, TransPharma may expand its development to include any number of these potential applications.

RF-MicroChannels, with their proven efficacy, suitability for an extremely large variety of drug molecules, well-known technology and low production costs, make them the ideal solution for pharmaceutical companies looking to find a viable and successful transdermal drug delivery system. TransPharma's unique patches are compatible with its delivery system, and offer potential pharmaceutical partners a comprehensive solution for transdermal drug development. Together, the flexibility of the ViaDerm drug delivery system enables the transdermal delivery of a wide range of drug products, offering a viable alternative to existing drug administration routes.



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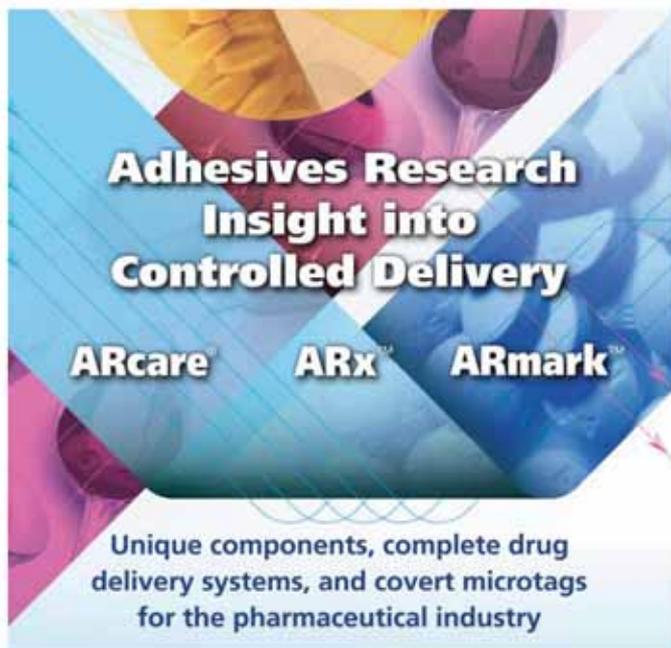
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# Custom Developer and Manufacturer of Dissolvable Films and Transdermal Platforms



## Corporate Description

Adhesives Research (AR) is one of the world's leading independent developers and manufacturers of pressure-sensitive adhesive (PSA) systems, custom-coated products, and specialty films. The company's three divisions develop platforms for drug delivery and brand protection. AR's range of services to support custom applications includes:

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- ARx™** complete drug delivery systems, including dissolvable films and transdermal tapes
- ARmark™** **Authentication Technologies** — covert microtags for product surety, brand protection, and risk mitigation

AR's custom development capabilities include polymer synthesis, adhesive mixing, compounding, coating, and release liner design, which are supported by analytical capabilities. The company integrates all of these capabilities to formulate and manufacture unique products to meet customers' specifications.

Our extensive analytical capabilities allow for the characterization and quantification of key product attributes during development and production of commercial materials. We maintain separate cGMP production facilities and follow applicable regulatory guidelines for the manufacture of oral and transdermal pharmaceutical delivery systems. Active drug master files are maintained and complete production records are accessible to support all clinical and commercial manufacturing requirements.

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- **Skin Contact PSAs** — customizable polyisobutylene (PIB) and acrylic chemistries for reservoir, matrix, and device-assisted transdermal and topical delivery systems
- **Conductive Films and Adhesives** — electrically and ionically conductive coatings for use in passive and device-assisted transdermal delivery systems
- **Stabilized Silicone PSAs** — provide chemistry that is synergistic with drug substances and conductive adhesives for drug delivery devices
- **Dissolvable and Erodable Chemistries** — can be tailored for oral or topical sustained release

**ARx™** offers custom-developed dissolvable film and adhesive platforms for:

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- **Transdermal Drug Delivery** — dissolvable and adhesive systems for topical and systemic delivery
- **Biopharmaceutical** — novel cast platforms for large molecule transdermal delivery

**ARmark™ Authentication Technologies** develops anti-counterfeiting technology in the form of covert markers that can be combined with custom-developed delivery systems for application to a variety of goods including pharmaceuticals and packaging. The covert ARmark™ markers are identified via digital micro-imaging hardware and customized software programs. The use of covert authentication markers to enhance product surety can:

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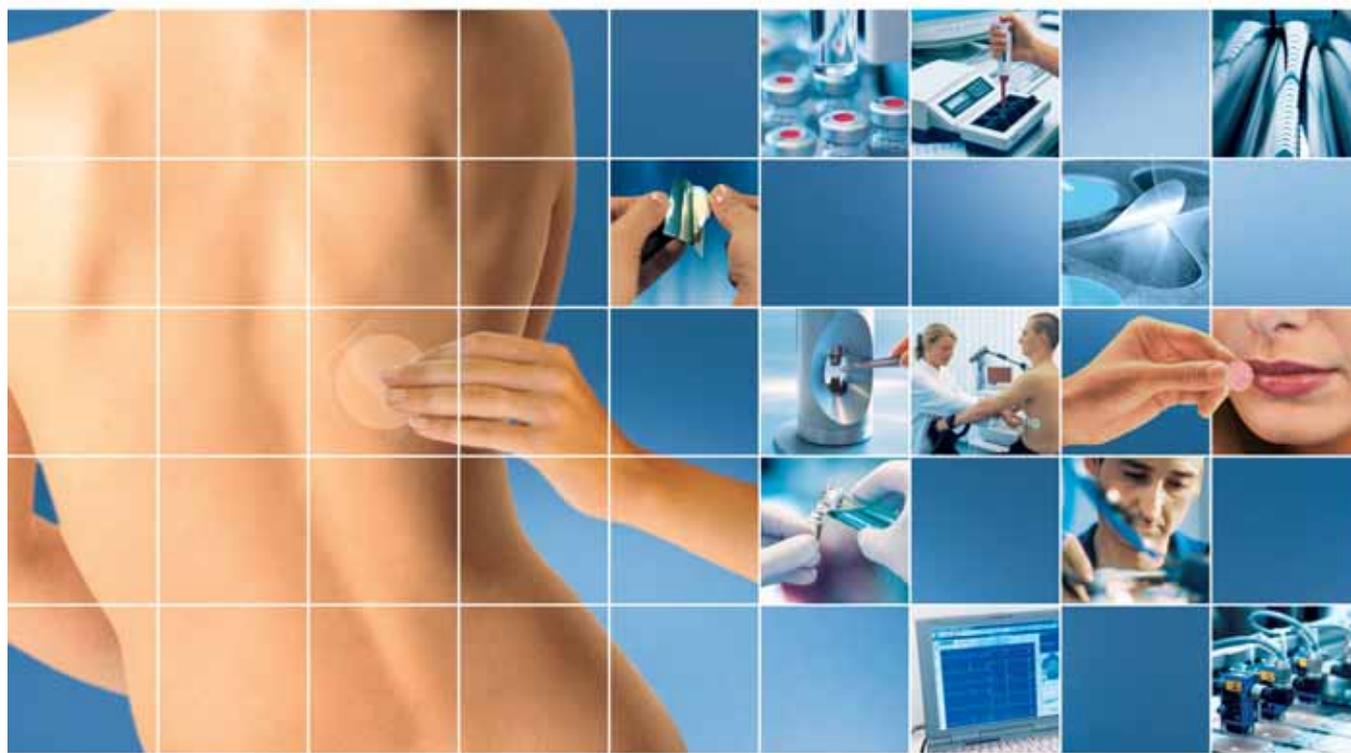
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# PASSPORT™ APOMORPHINE HCL PATCH: MEETING UNMET NEEDS IN MANAGEMENT OF PARKINSON'S DISEASE

Altea Therapeutics is currently in clinical development of a transdermal patch designed to address a major unmet need by preventing 'off' periods and provide an improved therapeutic option for managing Parkinson's disease. In this article, Yogi Patel, Manager of Business Development, and Steve Damon, Vice-President of Business Development, present an analysis of the disease from the patient's perspective. This type of analysis is essential for developing truly effective treatments.

Parkinson's disease is a progressive neurodegenerative disorder of the central nervous system that has a terrible impact on the quality-of-life of many of the approximately 4 million people affected worldwide.<sup>1</sup> The disease tends to affect both genders equally, and the initial symptoms typically appear when people are in their late fifties or early sixties. Since there is no cure for the disease, patients are prescribed medications mainly to alleviate their symptoms, a feat difficult to accomplish in late-stage disease as experienced by the patient below.

## A PATIENTS TESTIMONIAL: "TRAPPED IN MY OWN BODY"<sup>2</sup>

*My Parkinson symptoms make my life constantly frustrating.*

*There are so many things I can do and want to do – but at any given minute, I suddenly find myself unable to do them. My medications stop working or I am overcome with fatigue.*

*I worry about falling and breaking a hip or wrist, but I want to keep mobile. When my medication is working, I am able to move about safely with a walker, handrails and other aids.*

*Because of the tremor, the stiffness and the slowness of movement, sometimes I have real difficulties with simple tasks like brushing my hair, washing, getting to the toilet on time. It embarrasses me that I can't handle these personal matters as well.*

*I've had Parkinson's a long time, and the medications don't work smoothly or consistently. Often, quite unpredictably, I become extra slow, even immobile, and I just can't manage tasks that at other times don't cause trouble.*

*Often I have periods of jerky, involuntary movements. These are due to the length of time I have been on treatment. Even when the pills are doing the job, I may walk badly with a lurching or shuffling gait.*

*Sometimes for a short time, I literally "freeze" on the spot. A physiotherapist can demonstrate useful strategies to help me become unstuck; don't push me or pull me as this may lead to a fall.*

*Mealtimes in the dining room can be really frustrating and embarrassing. It takes me ages to cut my food and get it to my mouth. It is often cold before I am half through the meal. And over the years, I've also developed problems with swallowing. As a result, there is always too much saliva in my mouth and I drool. Very embarrassing. Also, because of the swallowing difficulties, I worry a lot about choking.*

*I get tired very easily. All voluntary movements take more effort for a person with Parkinson's. On the other hand, it is difficult for a Parkinsonian to get a good night sleep: I may need help turning over. If the medications wear off before morning, I awake feeling cramped and stiff, I can't move naturally in bed and it is impossible to fall back to sleep.*



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Clip Passport patch into the Applicator



Apply to skin and activate



Begin drug delivery

Figure 1: The PassPort™ System is simple and easy to use

*My face muscles don't work automatically any more, so unless I tell myself "smile", I may look grouchy or uninterested. But please ask me how I'm feeling because I still enjoy conversation. My speech is often difficult to understand: the words get slurred or muffled, and the volume is low because various muscle systems are affected. My slowness to respond does not mean I have a hearing problem or that my brain is slow – but my tongue muscles are!*

*Parkinson's is a very lonely and boring condition. Often I feel trapped in my own body.*

## PARKINSON'S DISEASE

Parkinson's disease is associated with the part of the brain responsible for coordinated movements and is caused by a loss of dopamine-producing cells in these areas. Often, the first symptom of Parkinson's disease is tremor (trembling or shaking) of the hands, arms, legs, jaw, and / or face. Other common symptoms include

rigidity or stiffness of the limbs and trunk, bradykinesia or slowness of movement, and postural instability or impaired balance and coordination. In severe cases, Parkinson's can lead to dementia, memory loss and other cognitive disturbances. Common complications of the disease include depression, difficulty chewing and swallowing, urinary problems, sleeplessness, injuries from falls, side effects of medications, and difficulty performing general activities of daily living. Medications for Parkinson's Disease also may cause a number of complications, including involuntary twitching or jerking movements of the muscles (dyskinesia), hallucinations, sleepiness, and a drop in blood pressure when standing up (orthostatic hypotension).

Parkinson's Disease not only causes severe burden on the patients but also on their family and loved ones. Patients often suffer disrupted family and personal relationships, withdraw from social activities and frequently suffer from depression (even from the earliest stages of the

disorder). As the disease progresses and deterioration increases, it usually has a negative impact on the entire family's quality-of-life and financial status.

In the United States alone, combined direct and indirect cost is estimated to exceed \$5.6 billion per year; medication costs for an individual patient average \$2,500 a year, and therapeutic surgery can cost up to \$100,000 dollars per patient. The greatest financial costs associated with Parkinson's disease can be attributed to loss of productivity followed closely by home-care and direct healthcare costs.<sup>3</sup>

## CURRENT TREATMENTS

At this time no treatment has been shown to slow or stop the progression of Parkinson's disease. Instead, therapy is directed at treating the symptoms that are most troublesome to a patient. Treatment approaches include medication and surgical therapy. Surgery is an option for patients that have severe, fast progressing disease and have failed on other therapies. Surgery, like other treatment options, helps with symptomatic control, and does not cure Parkinson's disease. Other treatment approaches include: general lifestyle modifications, physical therapy, and speech therapy.

The most effective therapy currently available for Parkinson's is levodopa, which remains the cornerstone of Parkinson's treatment. Nevertheless, the effectiveness of levodopa tends to diminish over time. After two to five years, 60- 80% of Parkinson's disease patients on levodopa experience fluctuations in response to their therapy.<sup>4</sup> Also, the most common side effects of levodopa include dyskinesias and other involuntary movements.

Other common drugs used to manage the symptoms of Parkinson's disease include Catechol-O-methyl transferase (COMT) inhibitors, anticholinergic agents, and monoamine oxidase (MAO-B) inhibitors.

Another class of drugs, known as dopamine receptor agonists, mimic the action of dopamine

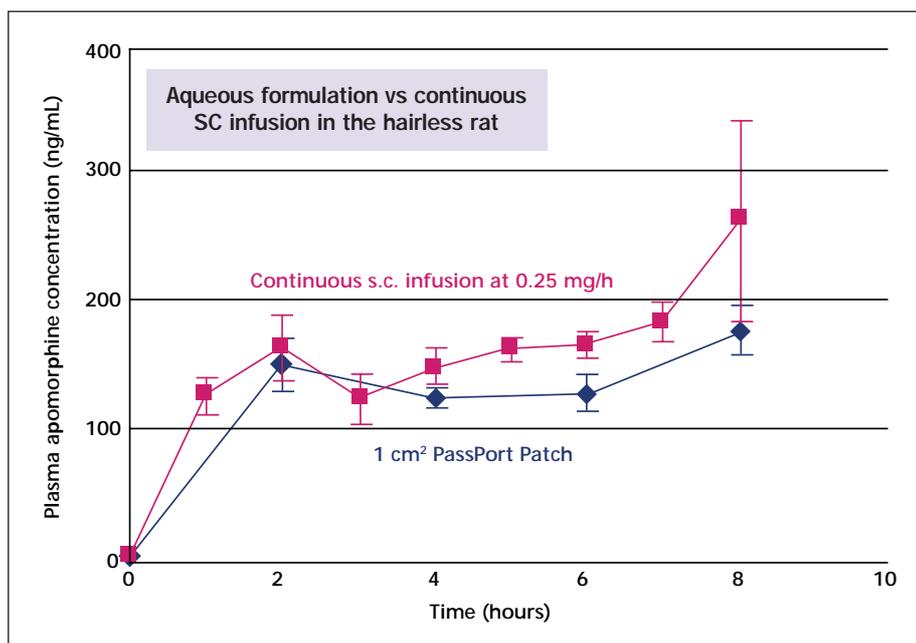


Figure 2: Apomorphine concentration (plasma) vs. time in hairless rats by (i) transdermal administration using the PassPort™ System and (ii) subcutaneous infusion

in the body. Dopamine agonists currently dominate the Parkinson's disease market due to the lack of efficacy of marketed brands from other drug classes which fail to provide long-lasting symptomatic relief. In addition, although levodopa (and other dopaminergics) have been widely used, recent studies suggest that dopamine agonists are a useful symptomatic long-term treatment for Parkinson's disease and that the early use of dopamine agonists reduces the incidence of motor complications as compared with levodopa.<sup>5</sup>

The various dopamine agonists differ in several respects, including chemical structure, duration of action, and side effects. The response to a particular dopamine agonist varies considerably between individuals, so that if one dopamine agonist does not offer benefit or causes bothersome side effects, another agonist may be tried.

### ALTEA THERAPEUTICS PASSPORT™ SYSTEM

Despite the enormous efforts toward finding a cure, symptomatic relief using various drugs remains the therapeutic cornerstone.

These drugs, although effective, do not provide complete resolution of symptoms. In fact, some medications result in side effects that are further debilitating for patients. The major unmet need in the treatment of advanced Parkinson's disease is the reduction of 'off' periods - frequent, prolonged, and/or unpredictable periods of hypomobility. Novel drug delivery mechanisms and formulations will become an increasingly important product differentiating strategy.<sup>6</sup>

Altea Therapeutics is developing a transdermal skin patch to provide continuous delivery of apomorphine for the prevention of 'off' periods and provide an improved option for the symptomatic management of Parkinson's disease.

The company's proprietary PassPort™ Patch is designed to deliver continuous levels of apomorphine over a sustained period of time from a skin patch ranging from 2 cm<sup>2</sup> to 8 cm<sup>2</sup> in size.

The PassPort System is painless and easy to use (Figure 1):

- Step 1: Clip PassPort Patch into the Applicator
- Step 2: Apply to skin and activate
- Step 3: Remove Applicator and begin drug delivery

Currently, the PassPort Apomorphine HCl Patch is undergoing Phase I clinical development. An initial Phase I pharmacokinetic study has demonstrated steady delivery of apomorphine over an eight-hour application period with rapid rise to

steady plasma levels and rapid elimination after patch removal. Preclinical studies have demonstrated transdermal delivery of apomorphine in hairless rats comparable with subcutaneous infusion (Figure 2). The patch provides constant therapeutic effect without interruption and thereby serves to replace injections completely.

The Applicator facilitates intuitive, accurate

and easy patch application. In addition, the Applicator stores verifiable dosing information, including a record of time and date for each successful patch application by the patient. This information may be accessed by the physician to monitor compliance – a critical tool in the management of Parkinson's disease, since only 10% of all patients are fully compliant with their prescribed therapy.<sup>7</sup>

### MARKET POTENTIAL

PassPort Apomorphine HCl represents an important opportunity for Altea Therapeutics in the management of Parkinson's Disease as it addresses the most significant unmet market need in managing the symptoms – the prevention of 'off' periods by a small, painless, and convenient skin patch. With the potential to provide a major improvement in the quality of life of Parkinson's patients, Altea expects to grow and capture a significant share of the market for Parkinson's disease therapy. The market for

drugs for the treatment of Parkinson's disease was US\$ 2.7 billion in 2005. Over the previous five years, the market has reported a growth rate of 12.9%. Dopamine agonists currently dominate the Parkinson's market - six out of the top nine marketed brands are dopamine agonists.<sup>5</sup>

Altea Therapeutics is actively looking for a



Altea Therapeutics' PassPort™ System

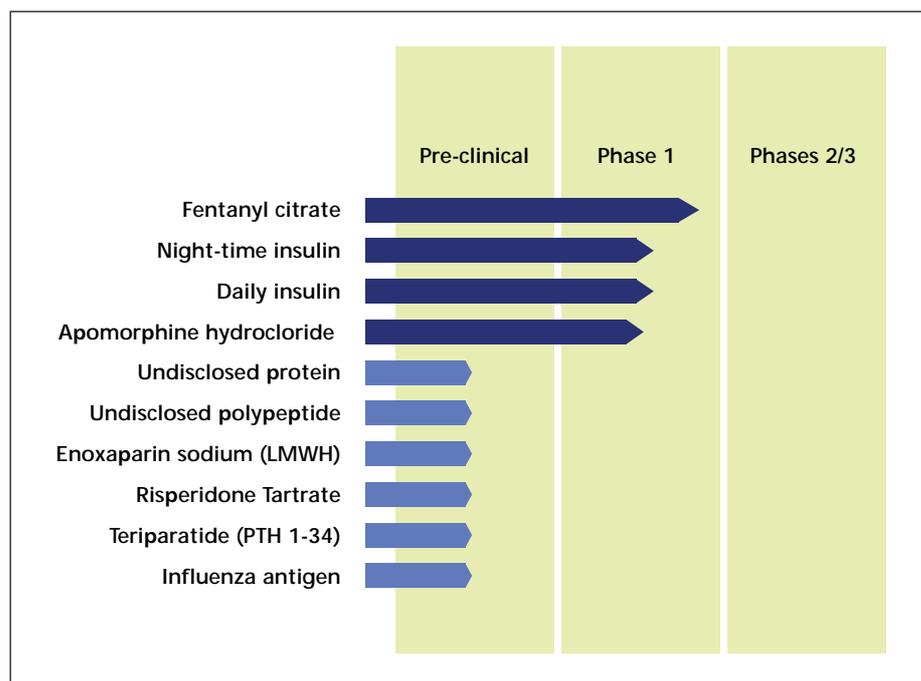


Figure 3: The Company's development pipeline attests to the ability of the PassPort™ System to deliver a wide variety of drugs and vaccines transdermally

development and commercialization partner who has the capability to support development and effectively market this exciting new therapy in the CNS / Parkinson's market.

## SUMMARY

Altea Therapeutics' new transdermal technology enables the sustained transdermal delivery of water-soluble drugs, peptides, proteins, and nucleotides from a painless and cost-effective skin patch. The PassPort System enables the affordable, non-invasive, painless, and controllable delivery of a wide range of drugs via the skin that cannot be delivered using conventional patches (Figure 3).

In addition to PassPort Apomorphine HCl, Altea Therapeutics is developing a 12-hour and 24-hour basal insulin patch for the management of diabetes and has demonstrated sustained and constant insulin delivery at therapeutic levels over a 12-hour application in healthy subjects. Clinical data from a phase I glucose clamp study show efficient delivery of insulin and a pharmacodynamic effect of transdermal insulin comparable to

subcutaneous injection of a long-acting insulin analog.

The Company is also in clinical development for a fentanyl citrate patch for management of moderate to severe pain. The fentanyl citrate patch is designed to incorporate layers of potential deterrents against product abuse, misuse, and diversion, and provides rapid and sustained delivery of a highly effective opioid, fentanyl citrate.

Furthermore, Altea Therapeutics is developing a low-molecular-weight heparin patch for prevention and acute treatment of thrombosis, an atypical antipsychotic patch for schizophrenia and related disorders, and an influenza vaccine patch.

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<sup>4</sup> "Commercial Insight: Parkinson's Disease." *Datamonitor*, 2004.

<sup>5</sup> Fox-Tucker J, "The CNS Market Outlook to 2011." *Business Insights*, 2005.

<sup>6</sup> "Stakeholder Opinions: Parkinson's Disease - Review of Key Commercial Opportunities in the Symptomatic Treatment Market." *Datamonitor*, 2006.

<sup>7</sup> Leopold NA et al. (2004) *Mov Disord* 19(5):513-17



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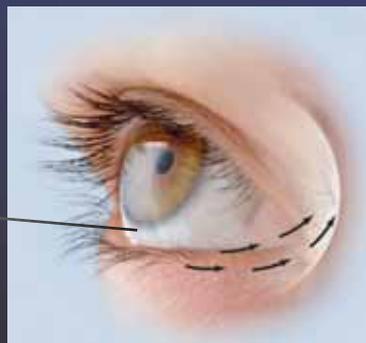
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## Transdermal

The PM2000<sup>™</sup> delivery system provides programmable bolus and baseline delivery capabilities



# Drug Delivery Systems Partnership Opportunities

IOMED, the first company to commercialize iontophoretic products, continues as a leader in developing new, non-invasive technologies and products that deliver drugs safely to areas of the body.

### Iontophoresis Applications

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# TRANSDERMAL PRODUCT DEVELOPMENT: FROM CONCEPT TO FULL-SCALE MANUFACTURING

**Corium develops, engineers, and manufactures drug delivery products and devices that utilise the skin as the primary means of transport. Its two proprietary technologies are the MicroCor™ mechanical microporation technology and the Corplex™ polymer technology.**

Corium is a privately-owned company engaged in the research, development and manufacture of advanced transdermal drug delivery technologies and products. Through the combination of its proprietary delivery technologies and its development and manufacturing expertise, Corium is developing a range of novel active and passive transdermal products.

Corium's self-funded product pipeline is based on high-value, FDA-approved drugs reformulated with Corium's proprietary systems. The products cover several therapeutic categories and are in various stages of clinical development. Corium plans to commercialize its products through partnerships with pharmaceutical and biotech companies. Corium also has several partner-funded products under development with small, medium and large pharmaceutical companies.

## SCIENTIFIC EXCELLENCE

Corium has complete technical capability ranging from concept, formulation and prototyping, to clinical supply manufacture and full scale manufacturing. Corium's proven processing experience is diverse and highly specialized and includes custom-designed liquid mix systems, continuous and semi-continuous extrusion, solvent and water-based coatings, specialized intermittent lamination, die cut and pouching equipment and customized vision systems for quality inspection.

Corium's R&D facilities, located at its Menlo Park, CA, US headquarters, are focused on basic and applied research, formulation,

pharmacokinetics and product development. Its process development and commercial manufacturing (pictured in figure 1) are located in two adjacent state-of-the-art manufacturing facilities in Grand Rapids, MI, US. These facilities are FDA, cGMP and DEA approved with ISO 9001, 2000 and 13485 certifications.

Corium's ability to move from concept to prototype to full-scale production includes:

- drug delivery research and development
- product design and process engineering
- prototype and pilot manufacturing
- clinical and commercial manufacturing

## MICROCORTM

MicroCor is a proprietary transdermal delivery technology consisting of an array of microstructures (see figure 2a), which mechanically create temporary micropores in the upper layers of the skin (see figure 2b). The microstructures can be fabricated from a variety of materials in varying lengths, offering significant flexibility in the depth of drug delivery.

This active transdermal technology allows larger molecules, such as peptides, proteins and vaccines, to flow through the skin and also provides for faster skin permeation of small molecules.

The MicroCor technology delivers drugs from an integrated transdermal patch in a self-administered, one-step, user-friendly process (see figure 2c).

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Figure 1: Corium’s process development and commercial manufacturing sites are FDA, cGMP and DEA approved with ISO 9001, 2000 and 13485 certifications.

**CORPLEX™**

Corplex is a versatile polymer technology that can be delivered in liquid to solid forms for numerous drug delivery product applications. It consists of a composite blend of polymers with unique adhesive, physical/chemical, and water absorbing properties. Corplex offers a range of hydrophilic to hydrophobic properties, enabling excellent adhesion to both dry and wet surfaces, and a variety of wear times (seconds to days).

This full range of capabilities offers significant benefits compared with existing pressure sensitive adhesives, which adhere poorly to moist skin and are not suitable for highly hydrated and soft biological tissue applications, such as oral mucosa. In contrast,

Corplex has superior adhesion and tensile strength. Corplex is highly compatible and can be integrated into various dosage forms, including MicroCor.

**INTELLECTUAL PROPERTY**

The current patent portfolio surrounding Corium’s technologies exceeds 150 issued and pending US and international patents. The Corplex patents cover the design and manufacture of adhesives and delivery systems, including polymer synthesis. The MicroCor portfolio covers the use, manufacture and design of the micro arrays as well as combination technologies. MicroCor was acquired from The Procter & Gamble Company in 2005 and has been significantly enhanced by Corium.



Figure 2: MicroCor comprises a microstructure array (a), which creates temporary micropores in skin (b). Application is a one-step, user-friendly process (c).

# Crossing the barrier

TransPharma Medical is a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing ViaDerm, a proprietary, breakthrough, active transdermal drug delivery system. The ViaDerm system consists of a reusable handheld electronic device and a disposable patch containing a drug.

## Unique advantages of the ViaDerm system:

- ◉ Enables the systemic delivery of exact and reproducible therapeutic doses of drug molecules
- ◉ Encourages patient compliance by providing a painless and easy-to-use administration route
- ◉ Expands the spectrum of molecules that can be delivered transdermally, including high molecular weight biologics
- ◉ Allows the incorporation of proteins and peptides in a proprietary dry form stable patch with no enhancers
- ◉ Designed for safe self-administration at home, with minimal training
- ◉ Designed in three sizes to support various applications
- ◉ Small, convenient, and cost-effective

