Advantages of Transdermal Delivery

• Avoids GI tract
  – Prevents first pass metabolism
  – Eliminates drug absorption issues with GI stasis
    • Common with migraine, prior gastric surgery, diabetes mellitus
  – Treats conditions associated with nausea and vomiting
• Reasonably constant delivery can be maintained (as opposed to peaks and valleys associated with oral and parenteral delivery)
• Reduces need for active administration (some patches applied for 7 days)
• For patches, dosing can be stopped by removal
• Easy to apply, convenient administration
Global transdermal market forecasted to grow from $21.5b in 2010 to $31.5b by 2015

Transdermal Delivery
Why it matters to Pharma

- Product line extensions – buprenorphine, rivastigmine, methylphenidate
- Delivery of NCEs with low bioavailability – rotigotine
- Effective delivery of NCEs for patients with GI conditions and/or symptoms
First Generation Transdermal Systems

• Suitable for low-molecular weight, lipophilic APIs which are efficacious at low doses
• Patches, gels, liquid sprays
• Delivery limited and controlled by stratum corneum

Second Generation Transdermal Systems

• Utilize chemical enhancers to increase skin permeability
• Balance must be achieved to optimize drug delivery and prevent skin irritation
• Testosterone Gel
  – AndroGel® – isopropyl myristate
  – Testim®- pentadecalactone
Testim vs AndroPatch® – PK

- Testim significantly increased testosterone and DHT serum concentrations from baseline compared to AndroPatch (2 patches)
  - Consistent findings at 30, 60, and 90 days


Testim vs AndroGel – PK

Testim provided 30% higher serum testosterone levels compared to AndroGel with a similar safety profile.

Testim Efficacy

<table>
<thead>
<tr>
<th>Days of Treatment</th>
<th>Lean Body Mass (Muscle) (kg)</th>
<th>Total Fat Mass (kg)</th>
<th>% Body Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>61.6</td>
<td>29.4</td>
<td>30.9</td>
</tr>
<tr>
<td>Day 90</td>
<td>63.3</td>
<td>28.6</td>
<td>29.8</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>↑ 1.6</td>
<td>↓ 0.8</td>
<td>↓ 1.1</td>
</tr>
</tbody>
</table>

At Day 90, mean increase from baseline in lean body mass and mean decreases from baseline in total fat mass and percent fat in Testim-treated patients was significant when compared to placebo-treated patients.

Safety – Skin Irritation Testim vs AndroPatch

The distribution of men with positive application-site irritation scores at 30 (open bars), 60 (green bars) and 90 days (red stippled bars).

There were significant differences (P<0.001) for each of the Testim vs Andropatch comparisons at each time.

McNicholas TA, Dean JD, Mueller H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int. 2003;91(1):69–74
Disadvantages

• Undesirable physical properties
  – Stickiness
  – Fragrance
• “Black box” warning of secondary exposure to testosterone
  – Adverse effect potential of transfer risk to children and women upon close contact with skin

Active Delivery

• Iontophoresis
• Non-cavitational ultrasound
• Microneedles

Goal of these delivery systems is to enhance delivery across the stratum corneum while protecting deeper, living tissues.
**Iontophoresis**

- Iontophoresis provides an electrical driving force for transport of compounds across stratum corneum
- Charged drugs are move via electrophoresis

**Iontophoresis Delivery Design and Optimization**

- In designing an iontophoretic delivery system:
  - Dose delivered, dosing frequency, and pharmacokinetic profile must be defined
  - Early studies identify metals for electrodes, power source, design of patch (integrated power source or attachable power source)
  - Formulation must be developed which allows ion delivery and protects skin
  - Optimization studies define ionic strength, formulation, current density, and patch size and shape
Optimization – Ionic Strength Parameters

• For iontophoresis to occur, the drug substance must be ionized
  – Both in solution and possess a charge

• Parameters affecting iontophoresis:
  – Molecular size and molecular weight of drug ion
    • Optimum range smaller and hydrophilic
  – Ionic strength and presence of other ions
    • If above range will decrease drug delivery as extraneous ions compete with drug ions
  – Influence of pH
    • If above range will increase risk of vascular reaction


Optimization – Current Density

• Current density is key factor in determining drug delivery, rate of delivery, and skin tolerability

• Current density is calculated by dividing current (usually in milliamps) divided by the drug delivery surface area (usually in cm²)

• Current density optimization studies must be conducted in vivo
  – Porcine model most effective for evaluating current density and tolerability issues
  – Studies should be conducted with formulation to be used in animal and human studies

Optimization – Size and Shape

- Optimization studies *in vitro* and *in vivo* investigate size and shape of:
  - Reservoir pad
    - Oval, circle, rectangle
  - Patch configuration
    - Oval, rectangle, figure 8
  - Electrodes
    - Oval, candelabra, rectangle, circle

Zecuity® Sumatriptan Iontophoretic Transdermal System

- Intelligent, active transdermal delivery
  - Microprocessor supports highly controlled and consistent delivery
    - Multiple safety checks within seconds of activation
    - Continuous feedback system throughout dosing interval
      - Controls both the rate and amount of drug delivered
      - No difference in PK regardless of age, race, or gender
  - Simple for patients – press a button (no inputs or adjustments)
Zecuity Sumatriptan Iontophoretic Transdermal System

Applied to upper arm or thigh.

Iontophoretic Device

Top View
- Fabric
- Activation Button
- Plastic Dome
- Batteries

Bottom View
- Foam
- Adhesive
- Electrodes
Reservoir Card

Zecuity Pharmacokinetics

Sumatriptan Plasma Concentration Group Mean (95%CI) Over Time
Zecuity Human Factors Usability Study

- Zecuity can be assembled, applied, and activated successfully during a mild to severe migraine attack
- In a clinical study, all participants (96.9% with moderate to severe migraine headache pain) were able to assemble, apply, and activate Zecuity
- Patients with migraine rated Zecuity very high for ease of assembly and ease of application/activation.

Zecuity Heat Study

- **External Heat Source:** A heat effect study in 12 healthy adult subjects demonstrated similar pharmacokinetic values without and with the application of an external heat source (40°C heat wrap placed over top of the ZECUITY TDS for the 4 hour dosing period).

![Sumatriptan Plasma Concentration Group Mean (95%CI) Over Time](image-url)
Zecuity Efficacy

• Pain relief and nausea freedom two-hours following patch activation
  – Twice as many patients treated with Zecuity achieve freedom from headache pain compared to placebo
  – 53% of patients treated with Zecuity achieved relief from headache pain compared with 29% for placebo
  – 84% of patients treated with Zecuity were nausea-free compared with 63% for placebo

Zecuity Safety

<table>
<thead>
<tr>
<th></th>
<th>Zecuity</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pain</td>
<td>26%</td>
<td>17%</td>
</tr>
<tr>
<td>Application site tingling</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>Application site itching</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Application site warmth</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Application site discomfort</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Allergic Contact Dermatitis (ACD)

- Defined as cases having higher irritation scores, a crescendo clinical course, or prolonged recovery
- Putative cases of ACD identified through medical safety review were combined with the cases reported as ACD
- For Zecuity, all putative cases were evaluated and classified by dermatology consultant and ACD specialist, Howard Maibach, MD, (University San Francisco)
  - ACD is expected diagnosis
- For Zecuity, two long-term study results where at least 2 patches were applied:
  - Probable = 3%
  - Probable and Possible = 8%

Transdermal Delivery and Pro-Drugs

- Prodrugs are an enabling technology to deliver drugs into circulation through the skin
- Transdermal delivery enables controlled and sustained drug release
- Pro-drugs may allow delivery of current medications that cannot be transdermally delivered and create new intellectual property
Novel advanced transdermal technologies


Conclusion

- Transdermal delivery is delivery system of the future
  - Viable alternative to oral or injectable administration
  - Non-invasive technology
  - Eliminate over or under dosing by continuous delivery of drug
  - Self-administration is possible