3. Ticarcillin-Clavulanate 3.1g (Timentin®)
   - Broad spectrum penicillin class antibiotic temporarily added to formulary to replace piperacillin-tazobactam (Tazidime®) due to a world-wide shortage of the latter product
   - The Division of Microbiology will be reporting antibacterial sensitivities to this drug

4. Piperacillin 2g, 3g vials (Pipracil®)
   - Broad spectrum penicillin class antibiotic
   - Refer to ticarcillin-clavulanate for more details

5. Estradot® patch
   - 17-ß estradiol transdermal patch to replace Estraderm® patch
   - See page 7 for review

Deletions

1. Acyclovir oral capsules (Zovirax®)
   - Alternative: Valacyclovir oral

2. Methyldopa injection (Aldomet®)
   - Discontinued by manufacturer

3. Estraderm® patches
   - Alternative: Estradot® patches

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Any comments, questions or concerns with the content of the newsletter should be directed to the editors. Write to CSU Pharmaceutical Sciences, Vancouver General Hospital, 855 W 12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email kshalans@vanhosp.bc.ca

Find us on the Web at www.vhpharmsci.com
Updated Policies/Procedures

1. Reduced Pharmacy Hours of Operation

Effective April 22, 2002, the VGH Pharmacy reduced its hours of operation and is open daily from 0630 hrs to 2400 hrs. Between the hours of 2400 and 0630, there is an on-call pharmacist who can be contacted for urgent requests that cannot wait until the pharmacy re-opens at 0630. A charge nurse or physician can contact the pharmacist via the switchboard at local 55000.

Wardstock requirements have been reviewed and modified for patient care areas. In addition, a Master Wardstock List has been placed in all areas that can be used to check which patient care areas have select medications as wardstock or in the night cupboard. To further ensure that all patients have access to medications that have been prescribed for them, please send all new prescriptions to pharmacy prior to 2130 hours. Prompt receipt of prescriptions will allow our pharmacists and pharmacy technicians to review the prescription for appropriateness, enter it into the patient medication profile, dispense the medication prior to our closure for the night, and print a computerized record (MAR) for designated units that accurately reflects the patient medication profile.

Thank you for your cooperation during this time.

2. Oral Acyclovir to Valacyclovir Interchange

Effective June 3, 2002, all orders for oral acyclovir will be automatically switched to valacyclovir at the equivalent daily dose (Table 1). The interchange is based on pharmacokinetic and clinical trial data. Valacyclovir is a prodrug of acyclovir with improved bioavailability, allowing extended interval dosing. This interchange applies to oral acyclovir only. If IV acyclovir is prescribed, it will be dispensed as prescribed.

<table>
<thead>
<tr>
<th>Oral Acyclovir Dose</th>
<th>Oral Valacyclovir Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1300mg/day</td>
<td>250mg PO BID</td>
</tr>
<tr>
<td>&gt;1300mg to &lt;4000mg/day</td>
<td>500mg PO BID</td>
</tr>
<tr>
<td>≥4000mg/day</td>
<td>1000mg PO TID</td>
</tr>
</tbody>
</table>

3. Parenteral Drug Therapy Manual (PDTM) and Y-Site Compatibility Chart 2002 Updates

VHHSC PDTMs and Y-site drug compatibility charts have been updated on all nursing units with the 2002 versions. Please contact Dr. Karen Shalansky, (604) 875-4839 if there are any questions regarding these items.

4. Revised Drug Administration Policies

The following changes have already been updated in the PDTM:

- After a baclofen test injection, temperature, pulse, respiratory rate, oxygen saturation and blood pressure must be monitored q30minutes x 2 post injection, then q1h until the patient is discharged.
- Fentanyl may be administered direct IV in the Burn Unit provided proper monitoring is carried out including: 1) a designated person whose responsibility is to monitor the patient’s vital signs and ventilation; 2) use of pulse oximeter and blood pressure monitor; and 3) readily available oxygen, bag and mask, and naloxone.
- The standard ketamine concentration for IV infusions will be 250mg/500mL IV fluid (0.5mg/mL).
- For prophylactic perioperative use of vancomycin, 250mg of the dose of vancomycin must be infused prior to skin incision.
- Streptomycin may be administered via IV intermittent in 100mL minibag over 30 minutes for the management of susceptible infections including tuberculosis and enterococcal synergy.
- Sufentanil may be administered sublingually for incident pain in any patient provided appropriate monitoring parameters are followed including sedation scale and respiratory rate every 5-10 minutes for 25 minutes after each dose. Drug data sheets are available from pharmacy for sublingual use.
- Ketorolac may be administered direct IV by nurses in Special and Critical Care Areas. On general nursing units, the direct IV route must be administered by a physician.
• Clarithromycin is no longer a restricted antibiotic and may be prescribed for susceptible infections including community-acquired pneumonia, Mycobacterium avium complex and Helicobacter pylori infections. Refer to page 6 for drug review.

5. Military Pharmacists’ Retraining

A recent graduate of the UBC Pharm.D. program is undergoing a special retraining work placement at the VGH Pharmaceutical Sciences CSU. This training has been arranged between the Department of National Defence and the Vancouver Coastal Health Authority. The objective is to assist Canadian Forces Health Service personnel to maintain their clinical skill set which is required to care for Canadian Forces personnel during overseas operations. To our knowledge, our pharmacy department is the first in BC to negotiate such an arrangement.

6. Anti-Infective Comparison Card Addendum

In the November 2001 Anti-Infective Comparison Card (update No. XIV), the ceftazidime susceptibility data were omitted during the printing process. The VHHSC susceptibility data for ceftazidime are as follows:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptibility to Ceftazidime</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>98%</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>99%</td>
</tr>
<tr>
<td>Serratia sp.</td>
<td>86%</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>99%</td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>Not determined</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>72%</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>88%</td>
</tr>
<tr>
<td>Acinetobacter baumanii</td>
<td>52%</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>77%</td>
</tr>
</tbody>
</table>

For more information, please contact the Division of Medical Microbiology at 54140 or CSU Pharmaceutical Sciences at 62481.

New Drug/Drug Products

1. Itraconazole Oral (Sporanox®)
   Tim Lau, Pharm.D.

Itraconazole is a triazole antifungal agent that exhibits the spectrum of activity seen with the earlier azoles, but is the only commercially available oral antifungal with additional activity against Aspergillus sp.1-3 The intravenous (IV) formulation of itraconazole is not available on the Canadian market and can only be obtained through the Special Access Program of Health Canada.

Oral itraconazole has been added to formulary primarily for the prophylaxis or treatment of aspergillus infections in patients who are unable to receive or tolerate IV amphotericin B.

Comparable Formulary Agents

Currently, amphotericin B IV, a polyene antifungal, is the only conventional formulary agent that can be used to treat aspergillus infections. Its use is limited by problems such as IV access requirements, infusion-related adverse effects (nausea and vomiting, fevers, rigors, and chills) and renal toxicity. In contrast, itraconazole can be administered orally and has a relatively more tolerable adverse effect profile.

In an open, randomized, equivalence trial, the efficacy and safety of IV followed by oral itraconazole has been compared with amphotericin B as empirical therapy for the management of 384 neutropenic patients with haematological malignancies.4 Itraconazole and amphotericin B were shown to have equivalent clinical efficacy (47% for itraconazole vs. 38% for amphotericin B), while fewer drug-related adverse events occurred in the itraconazole group (5% vs. 54%, respectively; p=0.001).

Itraconazole has also been investigated for the treatment of aspergillosis. In a small study using IV itraconazole for 14 days followed by itraconazole capsules for 12 weeks, 15 out of 31 patients (48%) responded to treatment.5 Most of the enrolled patients had hematological malignancies, while others had AIDS or chronic granulomatous diseases. The reported response rate was higher than that reported with amphotericin B in similar populations.2
Potential Risks
Adverse effects associated with the use of itraconazole include nausea (2-11%), vomiting (5-7%), diarrhea (3-11%), abdominal pain (1-6%), rash (1-9%), headache (1-4%), and hepatotoxicity (0-3%).3,6 Liver function tests are recommended for therapy exceeding 1 month. Itraconazole is also a potent inhibitor of cytochrome P450 3A isoenzyme and may modify the pharmacokinetics of other concurrent drugs that utilize the same metabolic pathway (e.g. cyclosporine and protease inhibitors).1

Potential Benefits
Oral itraconazole usage could potentially reduce the need for IV access and the use of premedications that are used with IV amphotericin B therapy. Additionally, itraconazole appears to have a more favourable adverse event profile. Itraconazole may also be used in patients with reduced renal function and could potentially reduce the usage of non-formulary amphotericin B liposomal and lipid complex products in itraconazole-susceptible fungal infections.

Cost
The use of oral itraconazole in place of IV amphotericin B for aspergillus infections would result in lower acquisition and administration costs associated with IV use (Table 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Itraconazole capsule</th>
<th>Itraconazole oral sol’n</th>
<th>Amphotericin B IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Regimen for Aspergillosis</td>
<td>200mg po q12h 200mg po q12h 70mg* IV q24h</td>
<td>70mg* IV q24h</td>
<td></td>
</tr>
</tbody>
</table>
| VHHSC Acquisition Cost (Daily Cost) | $4.12/100mg ($16.48) | $7.44/100mg ($29.76) | $37.35/50mg ($52.29)

*based on 1mg/kg regimen for 70kg patient

Dosage
The dosage of itraconazole for treatment and prevention of aspergillosis is 200mg TID x 3-4 days, followed by 200-400 mg/day x 3-4 months.3 Doses above 200mg/day should be given in 2 divided doses.

Itraconazole is available as a capsule and an oral solution. Food has differential effects on the absorption of itraconazole capsules and oral solution. The solubility of the capsule is aided by an acidic environment and absorption is optimal when taken after a full meal.2,6 Absorption is variable, however, in patients with damaged intestinal epithelium or with reduced acidity (e.g. achlorhydria, concomitant therapy with H-2 blockers [ranitidine] or proton pump inhibitors [omeprazole, pantoprazole]).1 In these situations, itraconazole oral solution has better bioavailability and is the preferred agent.2 Unlike the capsules, the oral solution should be taken on an empty stomach for maximal absorption.

Conclusions
Itraconazole is an effective triazole antifungal agent with coverage against a broad spectrum of fungi, including Aspergillus. It is orally administered and has a better tolerability profile and lower cost compared to IV amphotericin B. The capsule formulation should be taken after a full meal. The oral solution does not require an acidic environment for absorption and is preferable in patients with low acid states or damaged epithelium.

References

2. Valacyclovir Oral (Valtrex®)
Terryn Naumann, Pharm.D., Tim Lau, Pharm.D.

Valacyclovir is the L-valyl ester of acyclovir that is enzymatically converted to acyclovir after oral administration.1 Acyclovir exhibits antiviral activity against herpes simplex types 1 (HSV-1) and 2 (HSV-2), and varicella-zoster (VZV).1 Valacyclovir is indicated for the treatment of herpes zoster (shingles) and recurrent genital herpes, and for the suppression of recurrent genital herpes.2 At VGH, it will also be used for prevention of mucocutaneous HSV infections in immunocompromised patients.
Comparison to Oral Acyclovir (Zovirax®)

Since acyclovir is the active component of valacyclovir, both drugs have the same mechanism of action and antiviral activity. Valacyclovir has superior oral bioavailability (54% for valacyclovir vs. 10-20% for acyclovir) and can be administered less frequently (Table 1).¹

In a large, randomized, double-blind trial comparing valacyclovir (1000mg po TID x 7 days) to acyclovir (800mg po 5 times daily x 7 days) for the treatment of VZV in immunocompetent adults, valacyclovir recipients experienced a faster resolution of their zoster-associated pain (both acute pain and post-herpetic neuralgia).³ Median pain duration was 38 days for valacyclovir vs. 51 days for acyclovir, p=0.001. In those patients whose pain persisted for greater than 30 days (49% valacyclovir vs. 57% acyclovir), valacyclovir reduced the proportion of patients with pain persisting for at least 6 months, from 26 to 19%.

Valacyclovir (1000mg po BID) is as effective as acyclovir (200mg po 5 times/day) for treatment of recurrent genital HSV infections in otherwise healthy patients, reducing the time to lesion healing and the length of the episode.¹ Valacyclovir doses of 500mg po BID have also been shown to be as effective as 1000mg po BID for this indication.¹

Oral acyclovir is routinely used to prevent HSV infections in seropositive patients on the Leukemia/Stem Cell Transplant unit at VGH.⁵ A recent study conducted in this unit compared valacyclovir 250mg po BID and 500mg po BID to acyclovir 400mg po TID.⁴ This study concluded that the incidence of HSV infection was similar in all 3 treatment groups. In addition, patients who received valacyclovir were less likely to be switched to IV acyclovir than patients receiving oral acyclovir.

Potential Risks

The incidence of adverse effects with valacyclovir are similar to acyclovir and include nausea (10-16%), headache (13-17%), vomiting (7%), diarrhea (7%), and dizziness (6%).²

Potential Benefits

The less frequent administration of valacyclovir should result in lower overall costs (Table 1). The VGH study suggests that patients may better tolerate oral valacyclovir as a result of the less frequent dosing and a tablet formulation that is easier to swallow.³ Improved tolerance in these patients may result in lower drug costs as fewer patients would be required to switch to IV acyclovir.

Dosage

The dosage of valacyclovir is indication dependent.²³ Some representative regimens include:
- Herpes zoster: 1000mg TID x 7 days
- Recurrent genital herpes: 500mg BID x 5 days
- Suppression of genital herpes: 500-1000mg daily
- Prevention of mucocutaneous HSV infection in stem cell transplant: 250mg BID

Conclusions

Valacyclovir is at least as efficacious as acyclovir and may be more effective at reducing the duration of zoster-associated pain and post-herpetic neuralgia. Valacyclovir has better oral absorption and higher blood levels than acyclovir allowing for less frequent dosing.

References

3. Clarithromycin (Biaxin®)
Roxane Carr, Pharm.D., Tim Lau, Pharm.D., Karen Shalansky, Pharm.D.

Clarithromycin is a second generation macrolide antibiotic. Other macrolide antibiotics include erythromycin (first generation) and azithromycin (second generation). Clarithromycin was originally restricted at VHHSC for treatment of Mycobacterium avium complex (MAC) and Helicobacter pylori, but now can be prescribed for other susceptible infections as well.

**Pharmacology**
Macrolides act by reversibly binding to the 50S ribosome subunit of susceptible bacteria, inhibiting RNA dependent protein synthesis. Clarithromycin has activity against Streptococci, methicillin-sensitive Staphylococcus aureus, Moraxella catarrhalis, Haemophilus influenzae, Legionella, Chlamydia, Mycoplasma pneumoniae, and oral anaerobes (not Bacteroides). Although primarily bacteriostatic, clarithromycin may be bactericidal against some species such as Streptococcus pyogenes and Streptococcus pneumoniae.

Clarithromycin has a similar antibacterial spectrum to erythromycin, although it possesses better in vitro activity against H. influenzae and MAC.

**Indications for Use**
Clarithromycin is indicated in the treatment of acute exacerbations of chronic bronchitis, Helicobacter pylori (included in triple therapy regimens), sinusitis, Streptococcus pharyngitis, M. leprae, and for toxoplasmosis encephalitis (with pyrimethamine) and MAC in HIV positive patients.

Current consensus guidelines for the treatment of community-acquired pneumonia (CAP) recommend macrolides as one of the first-line agents for ambulatory patients. Ambulatory patients with CAP are most commonly infected with pneumococci or atypical organisms (M. pneumonia and Chlamydia). Second generation macrolides are recommended in ambulatory CAP patients with chronic obstructive lung disease where H. influenzae is more common. For patients with CAP that require hospitalization, empiric treatment for general medical unit patients should be aimed at pneumococcal pneumonia, H. influenzae, enteric gram negative bacilli, Chlamydia or Legionella sp. Monotherapy with levofloxacin, or combination therapy involving a 2nd or 3rd generation cephalosporin (e.g. cefuroxime) plus a macrolide antibiotic is recommended. For more severe cases of CAP requiring ICU admission, a macrolide plus a third generation cephalosporin (e.g. ceftriaxone) or a beta-lactam/beta-lactamase inhibitor (e.g. ticarcillin-clavulanate) is recommended. There is little evidence to support clinical superiority of clarithromycin over erythromycin in combination therapy.

**Pharmacokinetics**
The oral bioavailability of clarithromycin is 55% and its absorption is unaffected by food. Clarithromycin undergoes first pass metabolism to a 14-OH active metabolite. Metabolism of the drug is saturable via cytochrome P450 (CYP450). The half-life is 4-6 hours for the parent drug and 5-9 hours for the 14-OH metabolite. Similar to other macrolides, clarithromycin concentrates intracellularly, and tissue drug concentrations are often higher than serum concentrations. Dosage modification is required in renal failure.

**Adverse Drug Reactions/Drug Interactions**
Gastrointestinal (GI) intolerance (nausea, diarrhea, and abdominal pain) occurs less frequently with clarithromycin as compared to erythromycin (10.5% vs. 21.3%, respectively). In patients who are experiencing GI adverse effects due to erythromycin, clarithromycin may be better tolerated.

Both erythromycin and clarithromycin are cyp450 inhibitors and may thus cause increased levels of other drugs metabolized by the same system (e.g. warfarin, cyclosporine, tacrolimus, simvastatin, theophylline). CYP450 inducers, such as phenytoin, carbamazepine and rifampin may decrease clarithromycin serum and tissue drug concentrations.

**Dose and Cost**
The cost of clarithromycin is significantly greater compared to oral erythromycin (Table 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Erythromycin</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose for CAP</td>
<td>250-500mg po QID</td>
<td>250-500mg po BID</td>
</tr>
<tr>
<td>Daily Cost*</td>
<td>$0.16-0.33</td>
<td>$2.96-5.92</td>
</tr>
</tbody>
</table>

CAP = community acquired pneumonia
*based on VHHSC acquisition costs
Conclusion
Clarithromycin is no longer a restricted drug at VHHSC. While more expensive than erythromycin, clarithromycin offers a more convenient dosage schedule and improved GI tolerance for those intolerant to oral erythromycin. Although it is not available intravenously, clarithromycin would be a suitable agent for oral step-down therapy from IV erythromycin.

References
1. Israel D, Polk RE. Focus on clarithromycin and azithromycin: two new macrolide antibiotics. Hosp Formul 1992;27:115-34.

4. Estradot® Patch (Transdermal Estrogen)
Mey Ing E, B.Sc.(Pharm)

Transdermal administration of estrogen is an effective method for replacing estrogen in surgically or naturally induced estrogen deficiency states (menopause). Estradot® is replacing Estraderm® on formulary and is indicated for the relief of menopausal and postmenopausal symptoms (e.g. hot flashes, vulval and vaginal atrophy), and for the prevention of osteoporosis.

Pharmacology
17-ß estradiol is the principle estrogen produced by the premenopausal ovary but its production is diminished after menopause. The second major naturally occurring human estrogen is estrone which is derived from liver metabolism of 17-ß estradiol and from aromatization of androstenedione in adipose tissue. Unlike 17-ß estradiol, estrone levels remain relatively constant after menopause. The transdermal route avoids “first pass” metabolism and directly delivers estradiol through the skin into the bloodstream to the target organs resulting in a physiological circulating estradiol/estrone ratio of greater than 1 (normal values: >1 in premenopausal women, <1 in untreated menopausal women).

Transdermal Estrogen Products
The first generation transdermal reservoir system was introduced in 1985, and contains active estrogen in an alcohol gel reservoir. Estraderm® utilizes a first generation transdermal reservoir system to deliver 17-ß estradiol (Table 1). The estradiol is released through a semi-permeable membrane held against the skin by a ring of adhesive. Alcohol is used as a solubility enhancer which influences the absorption of estradiol, resulting in a gradual increase in estradiol levels over 2-3 days of wearing the patch followed by a decline. The alcohol contained in the patch is associated with skin irritation in a minority of women, causing a discontinuation rate of approximately 6%.

In the 1990’s, a newer generation matrix patch that incorporated estradiol into a matrix instead of a reservoir was developed. The matrix patch is devoid of alcohol and provides a more constant rate of drug delivery over the whole application.

Table 1. Comparison of Estradiol Transdermal Patches

<table>
<thead>
<tr>
<th>Product (Company)</th>
<th>Strength</th>
<th>Size</th>
<th>Delivery System</th>
<th>Frequency</th>
<th>Site of Application</th>
<th>Cost/50mcg patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estraderm® (Novartis)</td>
<td>25, 50, 100 mcg</td>
<td>5, 10, 20 cm²</td>
<td>Drug Reservoir</td>
<td>2 x weekly</td>
<td>Lower abdomen, buttocks, hip, side or lower back</td>
<td>$2.44</td>
</tr>
<tr>
<td>Estradot® (Novartis)</td>
<td>37.5, 50, 75, 100 mcg</td>
<td>3.75, 5, 7.5, 10 cm²</td>
<td>Matrix</td>
<td>2 x weekly</td>
<td>As above</td>
<td>$2.44</td>
</tr>
<tr>
<td>Vivelle® (Novartis)</td>
<td>37.5, 50, 75, 100 mcg</td>
<td>11, 14.5, 22, 29 cm²</td>
<td>Matrix</td>
<td>2 x weekly</td>
<td>As above</td>
<td>$2.44</td>
</tr>
<tr>
<td>Climara® (Berlex 3M)</td>
<td>25, 50, 75, 100 mcg</td>
<td>6.5, 12.5, 18.75, 25 cm²</td>
<td>Matrix</td>
<td>1 x weekly</td>
<td>Lower abdomen, upper buttocks</td>
<td>$2.44</td>
</tr>
<tr>
<td>Oesclim® (Fournier)</td>
<td>25, 50 mcg</td>
<td>11, 22 cm²</td>
<td>Matrix</td>
<td>2 x weekly</td>
<td>Buttocks, torso, upper arm or thigh</td>
<td>$2.44</td>
</tr>
</tbody>
</table>
period with less fluctuations of plasma estradiol levels. The difference in rate of absorption between the matrix and the reservoir system, however, does not have an impact on clinical efficacy as both have been shown to be equivalent with respect to the extent of estradiol absorption.\(^5\)

Various matrix patches are currently available (Table 1). A major advantage of the matrix system is the improved skin tolerability, comfort and adhesion.\(^3\) It may be particularly suitable for women who experience local sensitivity to alcohol-containing systems.\(^5,6\) As well, Estradot\(^\text{®}\) in particular is a much smaller patch compared to Estraderm\(^\text{®}\) (Table 1).

**Dosage/Cost**

Estradot\(^\text{®}\) 50mcg produces the same clinical effect on postmenopausal symptoms as 0.625mg of oral conjugated estrogens (e.g. Premarin\(^\text{®}\)).\(^7\) The Estradot patch can be cut in half if necessary for halving of the strength. The cost of Estradot\(^\text{®}\) is equivalent to Estraderm\(^\text{®}\) and other matrix patches.

For menopausal symptoms, treatment is usually initiated with the 50mcg patch and dosage adjusted according to symptoms.\(^8\) The patch is administered twice weekly, changed once every 3-4 days. Cyclic administration is recommended (21-25 days per month) unless the patient has had a hysterectomy or menopausal symptoms reappear during the treatment-free interval. In these situations, continuous, non-cyclic therapy may be indicated. In patients with an intact uterus, progestin should be sequentially co-administered for 12-14 days per cycle. The site of patch application should be rotated within a similar area of the body.

**Conclusion**

Estradot\(^\text{®}\) is a newer generation 17-ß estradiol matrix transdermal patch. Estradot does not contain alcohol and represents the smallest estrogen patch on the market. These factors may contribute to increased comfort and better tolerability compared to the Estraderm\(^\text{®}\) patch.

**References**