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EDITORIAL STAFF
Karen Shalansky, Pharm.D
Peter Loewen, Pharm.D.
Rubina Sunderji, Pharm.D.

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CHANGES TO FORMULARY

Additions

1. Tinzaparin 10,000IU/mL - 2mL vial (Innohep®)
   - low molecular weight heparin
   - restricted to treatment of deep vein thrombosis
   - Cost: refer to tinzaparin article, page 2

2. Nefazodone 100mg, 150mg, 200mg tablets (Serzone®)
   - antidepressant for management of refractory depression
   - Cost: refer to nefazodone article, page 5

3. Venlafaxine 37.5mg, 75mg tablets (Effexor®)
   - antidepressant for management of refractory depression
   - Cost: refer to venlafaxine article,

UPDATED POLICY AND PROCEDURES

1. Prescription Interpretation Policy (PIP)

The following PIPs have been added:

T if docusate is ordered with no strength indicated, the 100mg strength will be dispensed

T if urea cream is ordered with no strength indicated, the 10% strength will be dispensed

2. Therapeutic Interchange Program (TIP)

The following TIPs have been approved and are effective September 16, 1996.

* All orders for lorazepam oral will be
dispensed with the **sublingual dosage form** and labelled "for oral or sublingual administration"

*All current and new orders for **Centrum® Forte** will be interchanged to **Centrum® Junior Complete** (Banfield Extended Care and Discharge Planning Units only). Centrum® Junior Complete is similar to Centrum® Forte (Table 1) but is chewable and more palatable hence administration to residents/patients with swallowing difficulties will be facilitated.*

### Table 1. Comparison of Centrum® Forte to Centrum® Junior (Jr) Complete

<table>
<thead>
<tr>
<th></th>
<th>Centrum® Forte</th>
<th>Centrum® Jr Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betacarotene</td>
<td>1000 IU</td>
<td>5000 IU</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>4000 IU</td>
<td>2000 IU</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>30 IU</td>
<td>10 IU</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>90 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Folic acid</td>
<td>0.4 mg</td>
<td>0.1 mg</td>
</tr>
<tr>
<td>Vitamin B₁</td>
<td>2.25 mg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Vitamin B₂</td>
<td>2.6 mg</td>
<td>1.7 mg</td>
</tr>
<tr>
<td>Niacinamide</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>3 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Vitamin B₉</td>
<td>9 Fg</td>
<td>4 Fg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>400 IU</td>
<td>400 IU</td>
</tr>
<tr>
<td>Biotin</td>
<td>45 Fg</td>
<td>30 Fg</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>175 mg</td>
<td>162 mg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>125 mg</td>
<td>125 mg</td>
</tr>
<tr>
<td>Iodine</td>
<td>0.15 mg</td>
<td>0.15 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>10 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Copper</td>
<td>2 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Manganese</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>30 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Chlorine</td>
<td>27.2 mg</td>
<td>27.2 mg</td>
</tr>
<tr>
<td>Chromium</td>
<td>25 Fg</td>
<td>25 Fg</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>25 Fg</td>
<td>25 Fg</td>
</tr>
<tr>
<td>Selenium</td>
<td>25 Fg</td>
<td>25 Fg</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Nickel</td>
<td>5 Fg</td>
<td>5 Fg</td>
</tr>
</tbody>
</table>

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**Tinzaparivan for Treatment of Deep Vein Thrombosis**

**Introduction**

Tinzaparivan is one of three low molecular weight heparins (LMWH) available in Canada (Table 2). It has recently been added to the VHHS Formulary for the treatment of deep vein thrombosis (DVT). LMWH’s are obtained by depolymerization of unfractionated porcine heparin. Compared to unfractionated (traditional) heparin, LMWH’s are better absorbed subcutaneously (SC), have a longer duration of action, have a higher affinity for factor Xa, and require less laboratory monitoring.

### Table 2. Comparison of Low Molecular Weight Heparins to Unfractionated Heparin

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Tinzaparivin (Innohep®)</th>
<th>Dalteparin (Fragmin®)</th>
<th>Enoxaparivin (Lovenox®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Molecular Weight (range)</strong></td>
<td>15,000 d (5000-30,000)</td>
<td>4500 d (3000-6000)</td>
<td>5000 d (2000-9000)</td>
<td>4500 d (3000-6000)</td>
</tr>
<tr>
<td><strong>Anti-Xa: Anti-IIa ratio</strong></td>
<td>1:1</td>
<td>1.9:1</td>
<td>2:1</td>
<td>4:1</td>
</tr>
<tr>
<td><strong>Bioavailability (SC)</strong></td>
<td>30%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Peak Onset (SC)</strong></td>
<td>20-30 minutes</td>
<td>4-6 hours</td>
<td>4 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td><strong>Plasma t1/2 (minutes)</strong></td>
<td>60-150 (IV)</td>
<td>111</td>
<td>119-139</td>
<td>129-180</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>RES + Renal</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td><strong>Dose for DVT treatment</strong></td>
<td>Dosed to achieve 1.5-2.3 X aPTT</td>
<td>175 IU/kg SC daily</td>
<td>100 IU/kg SC BID</td>
<td>1mg/kg SC BID</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Availability</th>
<th>1000U/mL</th>
<th>10,000U/mL</th>
<th>5,000IU/0.2mL</th>
<th>30mg/0.2mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/5 day course</td>
<td>$26.02^{a,b}$</td>
<td>$68.64^a$</td>
<td>$132.30^a$</td>
<td>$228.08^a$</td>
</tr>
</tbody>
</table>

*RES = reticuloendothelial system*

*a VHHSC acquisition cost based on 70kg patient

*b based on 6000 U bolus, 1100U/hr

Comparative Studies: DVT Treatment

Several studies have compared dalteparin with heparin for DVT treatment.\(^{3-8}\) Despite differences in dalteparin administration (IV continuous infusion, SC), all studies demonstrated similar efficacy and incidence of bleeding complications compared to heparin.

There are two studies evaluating tinzaparin for DVT treatment.\(^9,10\) In a multicentre double-blind trial of 432 patients, Hull et al compared the effectiveness and safety of tinzaparin (175 units/kg SC daily to IV heparin (adjusted to maintain an aPTT 1.5-2.5 times the mean control value).\(^9\) Warfarin therapy was initiated on day 2 and continued for 3 months. Treatment with heparin or tinzaparin was discontinued on the sixth day of therapy provided the INR was greater than 2.0. Tinzaparin was found to be as effective as heparin (incidence of new episodes of venous thrombosis 2.8% and 6.9%, respectively). There were, however, significantly fewer episodes of early major bleeding in the tinzaparin group (0.5%) compared to heparin (5%). There was no significant difference in the incidence of thrombocytopenia defined as platelet count less than 150,000 (tinzaparin 2.8%, heparin 1.4%). In a smaller randomized trial, tinzaparin 150U/kg SC once daily was found to be equivalent to 75U/kg SC twice daily in preventing thrombosis progression in patients with venographically proven DVT.\(^10\)

Adverse Effects

Similar to unfractionated heparin, bleeding is the major adverse effect associated with LMWH.\(^11\) Protamine sulphate is the antidote for tinzaparin overdosage given at the same dosage as per heparin overdosage. Thrombocytopenia may also occur with LMWH (incidence < 3%). Heparin-induced thrombocytopenia (HIT) may be immune-mediated associated with antiplatelet antibodies. Kikta et al demonstrated that LMWHs had a high likelihood of causing platelet aggregation in patients who had heparin associated antiplatelet antibodies.\(^12\) Thus, LMWH’s cannot be recommended as a heparin substitute in patients with HIT.

LMWH may also cause transient elevations in hepatic aminotransferases and alkaline phosphatase, usually reaching a maximum within the first seven days of therapy.\(^13\) Other potential adverse effects of LMWH include rash (rare) and hematoma, bruising or pain at the subcutaneous injection site. LMWH has been reported to be successful in the treatment of a patient who developed osteoporosis while on unfractionated heparin, however inadequate data
precludes a useful comparison.  

Monitoring of Therapy

Initial studies recommended that plasma anti-Xa levels be monitored to assess efficacy of LMWHs. However, anti-Xa assays have not been shown to correspond well with the response of LMWHs and subsequent trials indicated that monitoring anti-Xa activity did not result in improved efficacy or safety. Baseline and twice weekly CBC (with platelets) is necessary for the duration of LMWH therapy; treatment should be discontinued if thrombocytopenia occurs.

Summary

Subcutaneous tinzaparin is a safe and effective alternative to IV heparin for the initial treatment of DVT. The once daily SC dosing and decreased laboratory monitoring could potentially lead to outpatient management of DVT. Despite higher acquisition costs of tinzaparin compared to heparin, the lack of laboratory monitoring of anticoagulant activity (e.g. aPTT) and costs associated with maintaining an IV infusion offset the additional costs of the drug. Due to the potential risk of bleeding and HIT, laboratory monitoring of CBC is still required during LMWH therapy.

There is limited data on LMWH for the treatment of pulmonary embolism. Until further studies are available, IV heparin infusions are still preferable in this patient population.

References

12. Kikta MJ et al. Can low molecular weight heparin and heparinoids be safely given to
Two New Formulary Antidepressants: Venlafaxine (Effexor®) and Nefazodone (Serzone®) are two new antidepressants recently added to VHHSC formulary for the treatment of depression resistant to traditional antidepressant therapy.

Venlafaxine (Effexor®)

Venlafaxine is an atypical antidepressant which is structurally unrelated to other antidepressants currently in use. Similar to tricyclic antidepressants (TCA), it inhibits the reuptake of both serotonin and norepinephrine. However, it does not have affinity for histamine, cholinergic, or alpha_{1}-adrenergic receptors, and thus has a reduced propensity to cause anticholinergic (dry mouth, constipation, urinary retention), CNS (sedation, anxiety), and cardiac (orthostatic hypotension, tachycardia) side effects.

Four randomized, double-blind comparative trials indicate that venlafaxine is at least as effective as imipramine, trazodone, and fluoxetine. One uncontrolled trial suggests that venlafaxine may be of benefit in a minority of patients with depression refractory to traditional antidepressants and electroconvulsive therapy (ECT).

Venlafaxine is well absorbed orally. It is extensively metabolized to an active metabolite which is renally excreted. The half-life of venlafaxine is 3-5 hours and its metabolite is 10-11 hours. Although it has been suggested that the onset of effect with venlafaxine may be more rapid (within 1-2 weeks) compared to other antidepressants, clinical data to support this assertion is sparse. Venlafaxine does not significantly affect the metabolism of other drugs.

Venlafaxine’s adverse effect profile is similar to that of selective serotonin reuptake inhibitors (SSRI) but with a higher incidence of nausea. Nausea is dose related and may be lessened with food. Common side effects include nausea (37%), somnolence (23%), headache (25%), dry mouth (22%), constipation (15%), and sweating (12%). Sustained mild hypertension is more common among patients receiving higher doses (> 225 mg/day).

The initial dose of venlafaxine is 75mg/day given in 2 doses which can be increased at 4 day intervals to the usual dosage range of 150-225mg/day. Dosage adjustments are necessary for both renal and hepatic impairment. Table 3 compares the cost of venlafaxine to other agents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose (mg/day)</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>20</td>
<td>$46.80</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>30</td>
<td>$50.70</td>
</tr>
<tr>
<td>Sertraline</td>
<td>100</td>
<td>$61.20</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100</td>
<td>$49.20</td>
</tr>
</tbody>
</table>
Amitriptyline | 100-150 | $0.60-0.90
Imipramine   | 150-200 | $3.60-4.32
Trazodone    | 200-300 | $35.40-53.10
Venlafaxine  | 150-225 | $58.80-88.20
Nefazodone   | 300-400 | $81.00-108.00

*a based on VHHSC acquisition costs

Nefazodone (Serzone®)

Nefazodone is a phenylpiperazine type antidepressant that is structurally related to trazodone. It inhibits serotonin reuptake post-synaptically and is also an antagonist at the 5-HT$_2$ receptor. Nefazodone possesses no anticholinergic or antihistaminic activity, suggesting it may be better tolerated than TCAs.

Blinded clinical studies have shown nefazodone to possess similar antidepressant activity to imipramine$^{11-15}$, sertraline$^{14}$ and paroxetine$^{15}$. Compared to amitriptyline, nefazodone’s antidepressant efficacy was found to be inferior$^{16}$. This may be due to the relatively small mean nefazodone dose used in this trial (242 mg/day). There are no trials comparing nefazodone to its closest relative, trazodone. As well, there are no published trials evaluating nefazodone’s efficacy in patients with depression refractory to other antidepressant agents.

Nefazodone is extensively metabolized resulting in an oral bioavailability of only 20%. The half-life of the parent drug is 2-4 hours and the half-lives of its three active metabolites range from 2-33 hours. As with other antidepressants, the onset of significant antidepressant effects does not usually occur before 3-5 weeks of therapy.$^{17}$ Improvement in depression-related anxiety symptoms and agitation may occur as early as one week into therapy.$^{18}$

The most common adverse effects of nefazodone include somnolence (25%), nausea (22%), dizziness (17%), constipation (14%), and lightheadedness (10%). Compared to SSRIs, nefazodone causes less sexual dysfunction, nervousness, insomnia, and tremors; however, it causes a higher rate of confusion, dizziness, and visual disturbances.$^{9,19}$ Nefazodone has not been reported to cause priapism, a serious side-effect of trazodone.

Dosage of nefazodone is initiated at 50-100mg BID which can be increased weekly to the usual dose of 300-500mg/day. Lower doses are suggested in the elderly and those with liver dysfunction. Nefazodone inhibits hepatic microsomal p450 3A4 enzymes, and has been shown in vivo to increase plasma levels of triazolam and alprazolam.$^{19}$ In both cases, the increased serum levels resulted in untoward effects. Through this same mechanism, there is a possibility for interaction with cyclosporine, midazolam, quinidine and nifedipine.

Conclusions

Both venlafaxine and nefazodone are atypical antidepressants which are generally well tolerated, are administered at least twice daily and are expensive. In the absence of data demonstrating the superiority of these agents over more established antidepressants, their use should be reserved for patients with depression who are intolerant to or have failed...
more traditional antidepressants.

References

Peter Loewen, Pharm.D.