Leo Pharma

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Venous Thromboembolism

• BMJ 12th March 2005:

• “VTE killed > 25,000 patients in England each year- more than combined deaths from breast cancer, AIDS and road traffic injuries combined”

• Many of these deaths are preventable
• DVT if not treated can cause PE and death
• But can also lead to post phlebitic leg syndrome, pulmonary hypertension etc.,
The LEO Foundation - Heritage

- LEO Pharma (1908) is wholly owned by the LEO Foundation
- LEO Pharma has NO shareholders
- The Company makes longterm decisions for ourselves, based on what we believe is right for the Company and for Patients
- 72 year History with Heparins, LMWHs and Protamine Sulphate
Therapeutic Area Sales 2013

Picato

Sales

Thrombosis
Dermatology
Other
LEO Pharma is the **only** LMWH manufacturer worldwide with control and oversight of the supply chain from mucosa to syringe.

LEO Pharma has systems in place which can trace the content of the syringe back to the pig mucosa or heparin from China is not approved by LEO for use in its heparin or LMWH supply chain.

LEO Pharma was the only heparin manufacturer with the analytical methodology and control strategy to prevent contaminated heparin from reaching the markets during the heparin crisis in 2008.

This analytical method was shared with regulatory authorities and consequently adopted in the USP Monograph for heparin sodium.
Experience and Safety

Innohep® was launched in 1991

Estimated > 83 million patient treatments since

Estimated approx 2.5 million Spanish patients treatments since

The safety profile of innohep® is well established

Very substantial data in special populations:

Renal Impairment

Cancer

Pregnancy

All 3 are growing High Risk therapeutic areas where LMWHs will be most important in future.
The very elderly are at greatest risk of VTE.
Elderly & Cancer patients have reduced renal function

Distribution of creatinine clearance by age


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innohep® is less dependent on renal clearance
It has more molecules with a longer chain length

Elimination: Tinzaparin is cleared through dual mechanisms

Tinzaparin (average MW 6.5 kDa)

In plasma

Binds to endothelial cell receptors more than other LMWHs

Clearance through both mechanisms

innohep® in elderly patients with renal impairment

innohep® (175 IU/kg) does not accumulate in elderly renal patients with CrCl > 20ml/min and thus no dose adjustment is required.

Reference:
Effect of molecular weight on Tissue Factor Pathway Inhibitor (TFPI) release from human endothelial cells

Reference:
TFPI also has a role in other important processes....

- **Anticoagulant role**
  - Thromboembolic disorders

- **Non-anticoagulant role**
  - Inflammation and angiogenesis in cancer
• A greater percentage of anti-Xa activity can be neutralised by protamine sulphate with Tinzaparin than enoxaparin and dalteparin (in vitro data)

The neutralisation of anti-Xa by protamine is strongly correlated with the total sulphate of the LMWH ($r^2=0.92$)
Thrombosis in Cancer

- Approximately 10% of patients with idiopathic VTE have underlying cancer\(^1\)
- VTE is the second most common cause of death in cancer patients\(^2\)

\(^2\) Adapted from Luxembourg B & Bauersachs R. VASA 2005;34:225-34
Thrombosis and Cancer Increases Risk of Death

Need For Improved Treatment of VTE in Cancer

- 20% of patients with cancer get a blood clot
- Blood clots are the 2\textsuperscript{nd} most common cause of death in cancer patients\textsuperscript{1}
- 60% of fatal PE in hospitalised patients with cancer had localised cancer, which would have allowed for reasonably long survival

\textsuperscript{1} Lopez JA et al. Hematology Am Soc Hematol Educ Program 2004; 439-56
The CATCH Study
Comparison of Acute treatments in Cancer Haemostasis

Goal

• Provide a once daily long-term treatment for cancer patients suffering from DVT & PE
  • Increase the scientific level of evidence

Although guidelines recommend to treat VTE patients for 3-6 months, the impact on current treatment has been limited

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### Summary of significant Tinzaparin cancer studies

<table>
<thead>
<tr>
<th>Author</th>
<th>No of cancer patients</th>
<th>Duration of treatment</th>
<th>Cancer type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al 2006 (LITE)</td>
<td>100/200</td>
<td>3 months</td>
<td>Mixed</td>
<td>Reduced recurrence at 12/12</td>
</tr>
<tr>
<td>Romera et al 2009</td>
<td>36/119*</td>
<td>6 months</td>
<td>Mixed</td>
<td>No sig difference in recurrence or bleeding</td>
</tr>
<tr>
<td>Daskalopoulos et al 2005</td>
<td>14/102*</td>
<td>6 months</td>
<td>Mixed</td>
<td>Fewer major events and greater recanalization with Tinzaparin</td>
</tr>
<tr>
<td>Dimakakos et al 2010</td>
<td>66/87 (DVT)</td>
<td>6 months (3pts for 3mths)</td>
<td>Mixed</td>
<td>No recurrent VTE for 2yrs f/u</td>
</tr>
<tr>
<td>Dimakakos et al 2010</td>
<td>14/26 (PE)</td>
<td>6 months</td>
<td>Mixed</td>
<td>No recurrent VTE for 2yrs f/u</td>
</tr>
<tr>
<td>Schmidt et al 2002</td>
<td>11</td>
<td>175IU/kg for 10/7 then 100IU/kg for 3/12</td>
<td>Malignant glioma</td>
<td>No bleeding, 2 recurrences</td>
</tr>
<tr>
<td>Leizorovicz et al 2011 (IRIS)</td>
<td>39/269*</td>
<td>Minimum of 5/7 then VKA for 90 days</td>
<td>Mixed</td>
<td>Bleeding and recurrence not significantly different but study stopped early</td>
</tr>
</tbody>
</table>

*No of cancer patients in tinzaparin arm of study*
LEO sponsored or supported VTE and Cancer studies

• **CATCH trial** – *Comparison of Acute Treatments in Cancer Haemostasis.* Randomised controlled trial comparing long term LMWH with VKA for 6 months.

• **TILT** study – *Tinzaparin In Lung Tumours,* Impact of adjuvant tinzaparin on survival in non-small cell lung cancer. Effect of innohep® on overall survival of patients with NSCLC stage I, II, or IIIA after complete surgical resection

• **PERI-OP** - Effect of perioperative standard vs extended thromboprophylaxis with innohep® on disease–free survival in patients with resectable colon cancer

• **Longheva** study – Open label randomised study of 6 or 12 month treatment with LMWH or VKA in cancer patients.

• **REALITY** - Real Life use of VTE treatment in cancer patients.

• **PELICAN** – Patient experience study in patients with CAT
innohep® is the LMWH which:

Is least effected by declining renal function  
*Important for safety especially in the elderly*

Gives the most anti IIa activity for standard doses  
*Important for efficacy for all patients*

Is most reversible with protamine sulphate  
*Important for safety*

Has substantial data in treatment of Pregnancy (safety, efficacy, PK)  
*Important for confidence in efficacy*

Has substantial data in management of VTE in Cancer…. with more soon  
*Important for confidence in clinical efficacy*

Is used once daily in all indications with no dose adjustments  
*Important for simplicity*

innohep® can be used – once daily **without dose adjustment** -in elderly, obese, renally-impaired*, and pregnant patients **Simplicity**

* with CrCl down to 20 ml/min