Recombinant Coagulation Factors 2015:

Maturation of recombinant clotting factor pipeline and emergence of gene therapy and alternative procoagulants

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Coagil VII is commercialized by Russian company Pharmstandard in the domestic market under tender assignment by the Russian government. Launch was in December 2010. Sales of Coagil VII in the year 2013 were RUB 2,652 mln (+78% vs previous year) corresponding to US$ 44.6 mln at the exchange rate of December 19, 2014 (Table 9 on page ) (Pharmstandard Annual Report 2013). Sales of Coagil VII posted by Pharmstandard are highly variable because they are generated by government procurement. In the first nine months of 2014, sales decreased by 54% compared with the same reporting period in the previous year (Pharmstandard Sales Results Oct 30, 2014). Sales of Coagil VII in 2012 were RUB 1,489 mln (-12.8%) and in 2011 were RUB 1,707 mln (-5.1%) (Pharmstandard Annual Report 2012). In the launch year 2010, Coagil VII was supplied for a total value of RUB 1,799 mln (Pharmstandard Annual Report 2011).

2.3.3 rFVII Market Size

The total market size of the two rFVII products in 2013 was US$ 1,566 mln, 4.9% higher than in the year 2012 (Table 10 on page ). Since 2005, the rFVIIa market developed with an average annual growth rate of 8.3% which is the highest continuous annual growth rate of the three different recombinant coagulation factor markets.

2.4 Recombinant Thrombin Product Sales and Market Size

During the full-year 2013, The Medicines Company obtained a global option to acquire Recothrom – the only marketed recombinant thrombin - from Bristol-Myers Squibb during a two-year commercialization license. The product generated sales of US$ 63.3 mln in 2013 (Table 11 on page ) (Press Release Feb 19, 2014). Recothrom 2012 sales were US$ 67 mln as reported by Bristol-Myers Squibb (TMC Annual Report 2012). In the first nine months of 2014, Recothromb generated revenues of US$ 46.5 mln (TMC Presentation Nov 5, 2014).
Turoctocog alfa and Advate were bioequivalent for all primary endpoints (incremental recovery, t½, AUC and Cl), and the secondary endpoints (AUClast and Cmax) were within the bioequivalence interval of 0.8-1.25. The half-life of turoctocag alfa was 10.83 ± 4.95 hours compared with 11.19 ± 3.51 hours of Advate.

New 3-year interim results were reported from Guardian 2, the extension of the pivotal Guardian clinical program (Press Release May 12, 2014). Guardian 2 is an open-label, multinational, single-arm extension trial involving 188 haemophilia A patients from 18 countries who had been previously enrolled in the Guardian 1 and Guardian 3 trials. Patients received NovoEight in a preventative regimen and to treat breakthrough bleeds. Interim results found (Ozelo, 2014a; Ozelo, 2014b):

- The overall estimated ABR achieved during preventative regimen with NovoEight was 1.7 (median 3.1) bleeds/patient/year, ranging from 1.4 (children aged 0-5) to 1.9 for adults (median number of bleeds/patient/year)
- Preventative regimen with NovoEight led to a decrease in ABR, followed by stabilisation at a lower level over the time period assessed.
- Mean preventative turoctocog alfa dose stabilized over time, with a tendency for gradual increase in patients ≥12 years, but the mean dose was on par with that reported for other FVIII products and within recommended range.

**Nuwiq; simoctocog alfa; human-cl rhFVIII**

In August 2014, the European Commission approved Octapharma’s Nuwiq (simoctocog alfa) for the treatment and prophylaxis of bleeding in all age groups with hemophilia A (congenital factor VIII deficiency) (Press Release Aug 6, 2014). Previously, the European Medicines Agency (EMA) had adopted a positive opinion towards human cell line recombinant human FVIII (human-cl rhFVIII), recommending the granting of a marketing authorization for the medicinal product for treatment and prophylaxis of bleeding (also during and after surgery) in pediatric and adult patients with haemophilia A (Press Release May 26, 2014). The marketing authorization
being developed for treatment of intracerebral hemorrhage, an acute emergency condition. Catalyst claims that its factor Xa variant has a higher potency and a longer half-life than the Pfizer molecule, but data have not been published.

Further down the coagulation cascade comes thrombin which is being studied by AstraZeneca in a big phase I trial with intravenous infusion. So far, it has not been disclosed for which bleeding disorder AstraZeneca would like to use recombinant thrombin. AstraZeneca also has disclosed results from a functional high throughput screening to find small molecules with procoagulant activity. It appers that the screening found some chemically diverse hits which were said to be used for creation of leads and further optimization toward oral bioavailability. If successful, this would result in a „tablet medication“ with the associated convenience advantage over parenteral administration regimens. But no update has been disclosed on this program.
collaboration started at the preclinical testing phase. Studies carried out by EpiVax and collaborators indicate that Tregitope may be useful for reducing the antibody formation (inducing tolerance) to transplants, protein drugs, and allergens by "Tregitopes" (de Groot, 2013; Jawa, 2013).

5.1.9  **The Medicines Company**

The Medicines Company took over from Bristol-Myers Squibb the commercialization of Recothrom, a topical recombinant thrombin product for use as a surgical hemostat. The product is being marketed in the US. As a complementary product candidate, The Medicines Company has acquired Dutch company ProFibrix, mainly because of their fibrinogen-thrombin combination product FibroCaps as a topical tissue sealant in a dry powder presentation format. The coagulation factors of FibroCaps are human plasma-derived. FibroCaps currently is under regulatory review by the FDA and the EMA.

**Table 58:  The Medicines Company Bleeding Disorder Product and R&D Pipeline**

<table>
<thead>
<tr>
<th>Drug name /INN</th>
<th>Indication</th>
<th>Product Characteristics</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recothrom; rhu thrombin</td>
<td>Surgical bleeding</td>
<td>Topical use for surgical bleeding</td>
<td>Market</td>
</tr>
<tr>
<td>Rhu fibrinogen</td>
<td>Surgical bleeding</td>
<td>Topical tissue sealant in combination with rhu thrombin</td>
<td>Preclinic</td>
</tr>
</tbody>
</table>

ProFibrix has brought to The Medicines Company a recombinant human fibrinogen project in preclinical stage which could be combined with the recombinant human fibrinogen to form a tissue sealant fully consisting of recombinant coagulation factors, the first of its kind.

5.2  **Big Pharma & Biotech as New Entrants to Bleeding Disorder Field**

5.2.1  **Biogen Idec**

Biogen Idec is the first biopharmaceutical company to have launched recombinant long-acting factor VIII and IX molecules in the US. Five months after launch into the US market, Alprolix (rFIXFc) had generated sales of US$ 35 mln and Eloctate (rFVIIIFc) posted revenues of US $ 22 mln in the first 10 weeks after launch mid July 2014. Both molecules have been approved by the
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