LEO Pharma **We help people achieve healthy skin**

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3rd April 2012
Ref. RNAUK

Appraisal consultation document (ACD) for rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

Dear Dr Adam

Thank you for the opportunity to comment on the ACD. Please see below LEO Pharma's comments.

Preliminary recommendation 3.2

LEO Pharma believes further clarity is required with regard to patients with renal impairment.

The EINSTEIN article[1] states that no dose modification is required regardless of renal function. LEO, however, believes there is little data within the published article to support this claim other than unsupported reference to subgroup analyses. Furthermore, the EINSTEIN extension protocol notes that one of the 'exclusion criteria in the study was a creatinine clearance of below 30ml/min', making it inappropriate for them to comment on poor renal function. It is of concern that patients have been included in the study which should have been excluded according to their protocol and raises the possibility of poor data quality assurance.

The use in patients with a creatinine clearance of less than 30ml/min corresponds to a level above which many LMWHs are licensed for use.

In contrast, there is specific and meaningful data to support the use of LMWHs such as tinzaparin sodium in patients with a creatinine clearance level of less than 30ml/min.

Preliminary recommendation 3.19

LEO Pharma agrees with the reservations expressed by the ERG about the population and

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interpretation of 'clinical equipoise' in the EINSTEIN-Ext trial, and the inclusion criteria used to assess clinical benefit.

The ERG recognised that there was a lack of clarity in the interpretation of clinical equipoise in the EINSTEIN-Ext trial. It is not clear from the published data under what type of circumstances equipoise would occur and no analysis was performed to determine whether this may have led to biased inclusion of patients into one or another arm of the study. It is possible that, in the main, there was little by way of clinical equipoise and consequently those patients for whom this was the case may not have been representative of the population as a whole. Again, it not possible to comment, as no clear analysis of this was presented and therefore there remains uncertainty as to the nature of the patient group included in the EINSTEIN-Ext trial.

Preliminary recommendation 3.22

As you are aware, all LEO heparin products are produced from porcine intestinal mucosa. As such this would normally make these products unsuitable for use in practising Muslim and Jewish patients, whose religious beliefs preclude them from using products derived from pigs.

However, during 2002, the Saudi Health Authority approved the use of innohep® (tinzaparin sodium), (as it is similar in its composition to human insulin that is porcine derived), by issuing a Fatwa (or official ruling) allowing its use in those patients requiring it for medical reasons. A copy of the letter (in Arabic) can be provided on request.

In addition, Gatrad AR and Sheikh A[2] discuss issues of medical ethics affecting Muslim patients. They state that:

"In the case of absolute necessity, where religiously lawful alternatives do not exist, Islamic teaching allows for Sacred Law to be suspended, temporarily if possible. The use of pork insulin and heart valves from pigs has been ruled acceptable by many Ulema on the basis of the principle."

We believe that this may also apply to the Jewish Faith.

LEO Pharma would therefore suggest amending the wording of this preliminary recommendation to reflect the above information.

Preliminary recommendation 4.3

LEO Pharma believes this recommendation needs further clarity. The recommendation currently states that "The Committee noted that unfractionated heparin was a comparator for rivaroxaban, but heard from the clinical specialists that unfractionated heparin is only used in people with renal failure". What data is the Committee referring to when noting unfractionated heparin was a comparator or is the Committee asking if it should be a comparator?

Yours sincerely,