COMMENTS ON MONONINE PRODUCT LICENCE APPLICATION - CPMP PL/0231/0097-102 - ARMOUR PHARMACEUTICALS

The Secretariat have identified the major issues associated with this application and I would generally support the draft recommendations.

In particular:-

- plasma screening procedures and plasma pool screening should conform to U.K. requirements.

- the monoclonal antibody used for purification should be treated as if it were itself a pharmaceutical product and should be required to conform to CPMP guidelines and the associated FDA 'points to consider' document.

- the manufacturer should be required to identify and validate the specific process step (thiocyanate incubation) which provides the necessary assurance of product viral safety and which can be pharmaceutically monitored and controlled. Partitioning of virus by chromatography will contribute to product safety but it's effect will be variable and difficult to control at scale. Similarly the use of high MW ultrafiltration membranes to physically remove virus is a complementary step in the over strategy but their is little experience of this technology which may be difficult to monitor and control within a routine manufacturing environment. The UK guidelines (BTS/NIBSC) require manufacturers to demonstrate that a single (controllable) process step is capable of inactivating > 5 logs HIV and Armour should be required to provide this assurance.

I would make the following additional comments:

(a) Throughout the application the company emphasise the quality advantages with 'high purity' FIX suggesting that purity is synonymous with low thrombogenic potential and reduced allo antigenic disturbance of immune function.

Some care is required when interpreting these claims. The company themselves present data comparing product derived from the "optimised process" and "non optimised process" which clearly demonstrates that high purity products such as Mononine can still have significant thrombogenic potential - probably as a result of contamination with FIX fragments (non IXa) which is co-purifying with intact FIX. It is therefore quite possible that it is the upstream initial purification procedure (DEAE chromatography) which determines product thrombogeniaty and <u>not</u> the immunopurification procedure. The manufacturer will require to exercise good control over this process step therefore.

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So far as allo antigenic effects on patients immune systems are concerned I am not aware of any data to substantiate these claims - though I recognise that this is currently the subject of debate in the scientific community and the market place.

(b) Mononine has been evaluated in vivo in a well established dog model (Edinburgh). This model measures the thrombogenic response to high doses of FIX using established biochemical markers such as F.P.A, FDP, fibrinogen, platelet levels etc.

Although only one batch has been evaluated the results would support the manufacturers claim that Mononine is non thrombogenic compared with traditional intermediate purity products.

GRO-C

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