

## ADVICE

### on the difficulties of producing solvent/detergent-treated plasma and on the arrangements for best meeting national therapeutic plasma needs

November 18, 2011

On November 10, 2011, the French Labour, Employment and Health Minister, consulted the Haut Conseil de la santé publique (French High Council for Public Health/HCSP) about the difficulties of producing solvent/detergent-treated plasma, with a view to proposing arrangements for best meeting national therapeutic plasma needs in this context.

The recommendations presented in this advice were drawn up by a specific working group bringing together experts from the HCSP's Patient Safety Committee as well as experts in all aspects of transfusion (prescribers, producers, infectious risk specialists and others associated with the use of labile blood products/LBPs). This working group interviewed representatives of the Agence française de sécurité sanitaire des produits de santé (French Health Products Safety Agency/Afssaps) and Établissement français du sang (French National Blood Service/EFS).

#### **The HCSP recalls the current context of the LBP transfusion chain:**

Just as in several other European countries, the founding principles of transfusion in France are based on free, anonymous and voluntary donations and on the principle of self-sufficiency. These principles are reiterated by the WHO World Health Assembly, European Union and Council of Europe.

LBPs have a special status setting them apart from medicinal products. This special status also explains the specific issuing and vigilance circuits (adverse effects resulting from their use are monitored through the haemovigilance circuit rather than the pharmacovigilance circuit).

Safety in the face of infectious risks (bacterial, viral and parasitic as well as non-conventional transmissible agents or prions) relies above all on a medical opinion prior to each donation (questionnaire, interview, succinct clinical examination) and highly effective biological examinations (blood tests, viral genome diagnoses) on the look-out for marks of infection by different pathogens; this is the only useable method to date that, from an infection perspective, can secure packed red blood cells (which account for the majority of transfused products).

#### **The HCSP also recalls the special conditions for securing and using therapeutic plasma:**

There are currently several methods for securing therapeutic plasmas either by quarantining plasma or inactivating pathogens through physico-chemical processes.

- Quarantining frozen plasma taken during an initial apheresis session and subjected to a series of tests for infectious purposes. The donor then attends a second check-up during which some of the tests for infection purposes are repeated. The plasma is declared fit for use only if both series of tests reveal negative results (quarantine plasma). This technique was widespread in France until 2008, and is still practised in Europe where it represents 70 to 80% of plasma production. The quarantine timeframe was initially set at 120 days; however, given the introduction of viral genome screening tests for HIV, HCV and HBV, Afssaps has recently authorised reduction of this timeframe to 60 days (Afssaps decision of October 19, 2011, published in the JORF [Official Gazette of the French Republic] of

November 6, 2011). This “native” plasma presents the best characteristics in terms of biological quality (fibrinogen and coagulation factors in particular).

- Treating plasma via methods that inactivate microorganisms – especially viruses (so-called viral inactivation methods) – is based, in France, on three processes that have been successively developed: solvent-detergent (SD plasma), methylene blue (MB plasma) and amotosalen (IA plasma). These three techniques are unequally used across different regions in France, and some of them are also used in other European countries.

The four forms of securing therapeutic plasma are authorised in France, even if quarantine plasma has no longer been offered by the healthcare sector since 2008.

MB plasma is also likely to disappear from the methods available to prescribers (by March 1 2012) following Afssaps’ decision (of October 10, published in the JORF of November 3, 2011) regarding the combination of too many allergic events being observed resulting from use of this MB-fresh frozen plasma (FFP) and the fibrinogen concentration measured in products. The allergies to methylene blue – exceptionally rare – are not fully explained, although arguments have been put forward casting doubt over MB treatment.

In view of its recent introduction, there is not enough hindsight to judge the tolerance (absence of allergic-type reactions for example) of IA plasma.

The availability of several types of FFP, according to the securing method, is recommended so as to be able to tackle the various situations that may be encountered as well (appearance of an adverse effect, supply disruption, etc.). Associated with the renowned level of safety achieved through quarantine, this argument explains why there is no recommendation for putting a definitive end to secured quarantine plasma. To sum up, the decision to stop making and distributing secured quarantine FFP in France has not been made because the risks genuinely outweigh the benefits from the recipient’s point of view. Rather, with a view to preventing an emerging infectious risk, a generic securing method has been chosen instead of one that focuses solely on the diseases detected.

The SD technique is the inactivation method in which we have the most experience. Although it reduces the risk of adverse effects of transfusion-related acute lung injury type plasma transfusion, it is the only one to be applied to groups of donations – which runs the additional risk of prion transmission. The size of these groups differs depending on the manufacturer: pools of 100 donations currently for the EFS in France versus 550 to 1500 donations for the two manufacturers holding the SD patent. In the industrial process, a final stage involving sifting through an absorption column is intended to reduce the prion risk, but more work is necessary to assess its efficacy.

The four aforementioned forms of secured plasma now have the same therapeutic indications, even if the quality of different products is not 100% equivalent – above all due to the partial alteration of some coagulation proteins with some so-called “viral inactivation” securing methods (SD, IA or MB).

LBP are preferentially distributed in the geographic region around the EFS and **Centre de transfusion sanguine des Armées (blood transfusion centre for military personnel/CTSA)** which sampled and treated them – even if there are relief circumstances between regions to guarantee self-sufficiency at national level. Prescribers are asked to have a diversified range of plasma at their disposal so that they can deal with all the clinical situations that may arise (allergies in particular). This justifies the decision not to recommend complete replacement of quarantine plasma by a single viral inactivation technique.

Plasma transfusion must also be analysed as part of a more comprehensive therapeutic strategy: plasma is rarely used alone but usually in combination with transfusions of packed red blood cells – a LBP category that cannot be subject to any viral inactivation.

**Lastly, the HCSP notes the current situation of therapeutic plasma production:** on the one hand, MB plasma is likely to disappear from the methods available to prescribers in the short term and, on the other, the one and only SD plasma production chain (Bordeaux EFS) is stricken with repeated infectious (environmental contamination) and technical problems (even though the

difficulties seem to have been resolved and the production chain is undergoing requalification at present).

In this context, the HCSP recommends:

- **favouring recourse to quarantine plasma to tackle a possible shortage of secured therapeutic plasma by the SD method, without rejecting the hypothesis of customised treatment – according to the SD technique – of plasma from voluntary donors who have given blood in France.**  
This is because quarantine plasma is a tried and tested solution with a very high level of safety today ; it is commonly practised across other EU countries and can be implemented quickly (plasma stocks can be released in the coming weeks after the requisite 60 days of “quarantine”) – thus chasing away the spectre of a shortage.
- **reviewing the situation over the coming months – apart from any emergency that might arise – and discussing the strategies for producing plasma (securing SD plasma production) and providing prescribers with a whole range of products to enable them to deal with any intolerances. These discussions may also involve European partners who share the same ethical values of giving blood.**

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#### Haut Conseil de la santé publique

14 avenue Duquesne 75350 Paris 07 SP FRANCE

[www.hcsp.fr](http://www.hcsp.fr)