Off-label use of intravenous immunoglobulins (IVIGs): funding mechanisms in France, Germany, Italy, Spain and the United Kingdom (EU5)

Charafii N (GFK, Melton Mowbray, UK); Gauthier-Dannis M (LFB Biomedicaments, Les Ulis, France); Conti C (GFK, London, UK)

Background
There has been substantial increase in the use of IVIGs in the EU5, particularly surrounding the funding challenges of off-label prescriptions. It has been carried out in May 2015 using PubMed, as well as websites of EU5 national healthcare agencies (table 2), using the following terms where appropriate: [off-label use OR unapproved] AND [intravenous immunoglobulin] AND [funding OR financing OR reimbursement].

Objective
The objective of the research was to describe and analyse how patients gain access to IVIGs for off-label indications in the EU5 and how the level of evidence may influence the funding of IVIGs when used off-label.

Methods
• A literature review was undertaken to understand the market access landscape of IVIGs in the EU5, particularly surrounding the funding challenges of off-label prescriptions.

Results
France
• Schemes allowing pragmatic solutions for the funding of off-label indications have been recently implemented in France through the granting of Temporary Recommendations for Use (RTUs).
• The French national regulatory agency (anam) may allow use off-label indications of medicines marketed in France if there is an unmet medical need and if the balance between efficacy and safety is presumed to be favourable to the medicine based on published scientific data. The anam will then develop an RTU, which will last for a maximum of three years, renewable. The objective of the RTU is to frame and control the conditions for use of this medicine thanks to a protocol allowing for collecting patient health outcomes.
• IVIG use off-label through RTU is funded or reimbursed (as it would be for an IVIG use on label), following HADS advice.
• However, as illustrated in table 3, while IVIGs do not benefit from an official RTU of the anam, they are still funded (on a case-by-case basis + proof of efficacy available in the scientific literature) when used off-label in France.

Germany
• Schemes allowing pragmatic solutions for the funding of off-label use have been recently established in Germany with the implementation of BARMF off-label expert group.
• The BARMF off-label expert group, on behalf of the G-BA, elaborates recommendation for “prescribable” off-label use. The Statutory Health Insurances (SHI) cover the off-label use of a medicine only if the medicine: is listed in Pharmacological adviser, annex VI used as part of a clinical trial to which the G-BA has not objected is used to treat a serious, life-threatening disease or one that impairs the long-term quality of life, for which no alternative is available and has proof of efficacy. IVIGs off-label use is recognised in Germany for two indications. Indeed, IVIGs are listed in the annex VI of the Pharmacological Directive for: polymyositis and dermatomyositis in adults, as an aid-on-therapy myasthenia gravis
• However, desk research did not allow for understanding:
  - if the BARMF off-label group replaces the PEI for the evaluation of off-label usage of IVIG
  - if and how IVIGs were still funded when used outside the G-BA framework

Italy
• Schemes allowing pragmatic solutions for the funding of off-label use have been recently changed in Italy by the law 79/2014 (May 21, 2014). Under the new law, Italy’s medicines agency AIFA will now, in some cases, permit off-label drug use if its reimbursement is decided upon by an Alternative Authorised Treatment (AAT). Previously, use was reimbursable only if the product was included in AIFA’s approved drug list (“liste di farmaci off-label”) and where no alternative authorised treatment was available.
• This law has been introduced for financial reasons, particularly to promote the use of cheap Lucentis (recombinant) instead of expensive Avastin (bevacizumab) for the treatment of wet macular degeneration.
• However, it appears IVIGs’ off-label use is not officially recognised since IVIGs do not appear in the “liste di farmaci off-label” and no record of AIFA’s authorisation for such use has been found.
• However, desk research did not allow for understanding and if how IVIGs were still funded when needed outside of AIFA’s framework.

Spain
• There is evidence of funding for IVIGs off-label use in Spain, but no specific schemes are set up as of September 2015.
• The desk research did not allow for understanding if and how IVIGs were used off-label in Spain.

United Kingdom
• In 2006, the Department of Health (DH) initiated a review to assess the opportunities available to secure the supply of IVIGs in the UK and to develop a more evidence-based approach to IVIG use. Following this review, a national Demand Management Programme has been introduced to provide guidance on the appropriate use of IVIGs. These uses have since been classified using a colour coding as described on table 4.

Conclusions
• IVIG’s off-label use funding is not equally regarded in the EU5. Only in France, Germany and the UK does a funding system exist for recognised off-label use of IVIGs.
• Harmonisation of off-label use funding, dependent on the level of evidence available as implemented in the UK, should be considered in the UK, and collect patient outcomes following off-label use of IVIG, as framed in the French system.