Annex IV

Conditions to the marketing authorisation

Conditions to the marketing authorisation(s)

The marketing authorisation holders shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

A visual reminder on the outer package to warn patient about the harm to unborn baby and the need for effective contraception when using the medicinal product should be implemented in all medicinal products containing substances related to valproate. The details of the visual reminder should be agreed at national level and be subject to a user test taking into account input from local patient representatives.	Within 3 months after Commission decision
The MAHs of medicinal products with substances related to valproate shall perform a drug utilisation study to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate. MAHs are encouraged to extend the ongoing drug utilisation study (DUS). Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC : Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	 Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol. Within 48 months after endorsement of the study protocol
The MAHs of medicinal products with substances related to valproate shall develop and submit educational materials according to agreed core elements. These materials should ensure that prescriber are informed and the patients understand and acknowledge the risks associated with valproate in-utero exposure. These should be submitted to the National Competent Authorities:	 Within 1 month of the Commission decision.
The MAHs of medicinal products with substances related to valproate shall conduct an observational study to evaluate and identify the best practices for switching of valproate in clinical practice.	

Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC : Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	Within 6 months after Commission decision Within 12 months after endorsement of the study protocol. Within 48 months after endorsement of the study protocol
The MAHs of medicinal products with substances related to valproate shall perform a survey among HCP to assess knowledge of HCP and behaviour with regard to PPP as well as receipt/use of DHPC and educational materials. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The final study report shall be submitted to the PRAC:	 Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol.
The MAHs of medicinal products with substances related to valproate shall perform a survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The final study report shall be submitted to the PRAC:	 Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol.
The MAHs of medicinal products with substances related to valproate shall conduct a PASS preferably based on existing registries to further characterise the foetal anticonvulsant syndrome in children with valproate *in utero* exposure as compared to other anti-epileptic drugs. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC :	 Within 6 months after Commission decision Within 12 months after endorsement of the study protocol.

Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	 Within 48 months after endorsement of the study protocol
The MAHs of medicinal products with substances related to valproate shall conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC : Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	 Within 6 months after Commission decision Within 12 months after endorsement of the study protocol. Within 48 months after endorsement of the study protocol
All MAHs should have in place a Risk management plan (RMP).	Within 3 months after Commission decision

With regards to the studies abovementioned, the MAHs are strongly encouraged to collaborate and perform joint studies.