MEANING AND IMPLICATIONS OF THE STUDY RESULTS

1.1 REGIONAL VARIATIONS

This study observed different levels and types of prescribing in the four different regions and notably even within the two different regions of Italy. This indicates that this study may not be representative of the extent and type of prescribing taking place in other European Union Member States.

1.2 INDICATIONS FOR PRESCRIBING

This study has demonstrated that, in addition to epilepsy, AEDs are now being increasingly prescribed for other indications including psychiatry conditions, such as bipolar disorder and anxiety, neuropathic and general pain and migraine. This means that it is important that data to evaluate the safety of AEDs are captured for the full range of indications using electronic healthcare data and study cohorts such as those of EUROmediCAT [54] in addition to disease specific registries. It is also important that all prescribing advice and warnings in addition to any interventions are made apparent to all potentially relevant prescribers, medical specialties, pharmacists and AED users and are not restricted to having the emphasis put on a particular indication. A French study has identified a higher risk of major congenital malformations following exposure to valproate for the treatment of epilepsy compared to valproate for the treatment of bipolar disorder[52] . Therefore the indication for prescription should be considered when evaluating safety.

1.3 PRESCRIPTIONS FOR GABAPENTIN AND PREGABALIN

The rapid increases observed in the prescribing of gabapentin and pregabalin in women of childbearing age and specifically during pregnancy together with evidence that these AEDs have the potential for abuse [55], means that the utilisation of these products requires future monitoring. In 2012, it was reported that there were no systematic studies to date on the pharmacokinetics of gabapentin or pregabalin during the course of pregnancy and that the consequences of prenatal exposure is inconclusive.[56] Studies in rats, however, have shown adverse effects on embryo-fetal development.[57] Therefore further investigations into their use and safety in pregnancy are should be performed.

1.4 PRESCRIPTIONS FOR VALPROATE

There is considerable evidence of valproate teratogenicity, both in terms of congenital malformations and longer-term neurodevelopmental disorders, with the teratogenic effects occuring early in pregnancy, often before a woman realises she is pregnant. The two facts that (i) valproate was the most commonly prescribed AED to the youngest age group (10-14

years) in every region and (ii) valproate was the most common AED taken during pregnancy by women under 25 years of age in all regions apart from the UK are of great concern. High levels of valproate prescribing in young females are likely to increase the risk of pregnancies being exposed to valproate due to a large proportion of pregnancies being unplanned[58]. However, there was evidence that the incidence of valproate prescribing had decreased over time in all regions, although the decreases had occurred to a greater extent in the older women. There was also evidence that the proportion of pregnancies exposed to Valproate was lower from 2012-2016 than from 2007-2011 for all regions apart from Tuscany where the prevalence remained the same. The prevalence of valproate exposure from 2012-2016 during the first trimester of 0.3 per 1,000 in Emilia Romagna, 1.5 per 1,000 in Tuscany, 0.7 per 1,000 in the UK and 1 per 1,000 in France present unacceptably high risks to the fetuses.
It is important to continue to try to reduce starting prescribing valproate to all women of child bearing age, particularly young girls and to encourage all women of child bearing age to switch to alternative AEDS. In July 2017 in France, prescription rules have been modified for valproate for psychiatric conditions (especially bipolar disorders). It is now contra-indicated in pregnancy and in women of child bearing age without an effective contraception

1.5 SWITCHING AED MEDICATIONS

There was no evidence of greater switching from valproate than from other AEDs, apart from a slight indication in France and the UK that there was more switching from valproate than other monotherapy AEDs in the years before pregnancy. In all regions switching was more common in the years preceding pregnancy than during pregnancy. In pregnancy switching is not recommended particularly as during pregnancy changes are experienced in pharmacokinetics and endocrine and electrolyte balance that may increase the risk of seizures.[59, 60] Females and their healthcare providers therefore need to weigh up the potential risks and benefits of treatment because poor seizure control during pregnancy can also pose considerable risks to both the mother and the fetus.

UNANSWERED QUESTIONS AND POSSIBLE FUTURE RESEARCH

This study has demonstrated that AEDs are now increasingly prescribed for a number of indications in addition to epilepsy. Therefore work is needed on investigating the association between the indication for prescribing and the risk of adverse pregnancy outcomes following in utero exposure. In addition more information is needed on the safety in pregnancy of the new AEDs, particularly for pregabalin and gabapentin.

This study identified a very large percentage of females of childbearing age who received only a single AED prescription during the ten year study period. Future work could look into this

type of one-off prescribing further in order to determine whether it is appropriate and whether the extent of it could be reduced.

This study did not look at the use of contraception among females of childbearing age receiving prescriptions for valproate or other AEDs and information on this could be of benefit for helping to determine the true size of the population considered ‘at risk’.