**Epilepsy Ireland Valproate Survey**
**December 2019 – February 2020**
**Summary Findings: July 2020**

## Background

In 2015 and 2016, Epilepsy Ireland conducted three surveys of women, girls, and their patients and carers, who were taking the anti-epileptic drug (AED) sodium valproate (Epilim).

This was undertaken to measure the impact in Ireland of new European Medicines Agency (EMA) guidelines issued in 2014 to reduce the risk associated with taking valproate during pregnancy.

Valproate can cause birth defects and development/ learning delays in children exposed to the medicine in-utero. Evidence shows that up to 30-40% of children will experience serious developmental disorders and approximately 10% will have congenital malformations.

The 2015-16 surveys found that there were some improvements over time in both patient awareness of the risks of valproate and in communication between patients and professionals on the issue:

- The percentage of respondents who were aware of the risks prior to taking the surveys increased from 33% to 79%.
- The percentage of women who said they had discussion about valproate risks/ restrictions increased from 11% in April 2015 to 56% in December 2016.

In December 2016, the Epilepsy Ireland report concluded: "*We believe that more should and can be done to improve awareness and communication further. We want to see further improvement from 56% who state that their HCP discussed valproate risks with them at medical appointments. We believe that every women or parent of a girl on valproate should have had discussions with their team since the EMA rulings on valproate over 2 years ago*".

Following a wide-ranging Europe-wide consultation process on the impact of the 2014 measures, the EMA introduced new restrictions from February 2018 and these have been implemented in Ireland by the Health Products Regulatory Authority. The 2018 measures include:

- Changes to the product information leaflet for patients and Summary of Product Characteristics for healthcare professionals
- Updated Educational Materials for patients and doctors, including a new patient alert card for pharmacists to provide to patients.
- Visual warnings on the packaging of valproate-containing medicines.
- Valproate must be initiated by a specialist and must not be used in girls and women who may be able to have children unless the terms of a pregnancy prevention programme (PPP) are followed. As part of the PPP, the prescriber must make sure the woman or girl understands the risk if

she became pregnant while taking the medicine. Women must also be aware of the need to take contraception while on valproate. A risk acknowledgement form must be completed and signed during a review, which must take place at least once a year.

Other measures undertaken in Ireland included a change in the pack size to eliminate broken bulk dispensing. The HSE also established a Valproate Response Project which, among other projects initiated the following risk-management actions:

- Direct communications with women currently taking valproate and their GPs, as identified by PCRS data (Summer 2018).
- The establishment of a Programme for Women's Health in Epilepsy to oversee the roll-out of EMA and HPRA mandated measures. This included funding for the Irish Epilepsy & Pregnancy Register and the approval of six Advanced Nurse Specialist posts. However, to date, only two posts have been recruited. Similarly, a new consultant post to oversee implementation of the Programme is also outstanding.
- A National Sodium Valproate conference in March 2019.

In December 2019, Epilepsy Ireland conducted another survey of women who have taken or who are taking valproate, since the introduction of the PPP. We have surveyed women who have taken valproate since 1 August 2018, and who therefore should have seen a health professional in that time.

The aim was to measure patients' awareness of the risk of valproate in pregnancy and to understand the impact that the above HSE and HPRA changes have had on risk communication and patient care.

The questionnaire used was based on a similar survey being undertaken in the UK by three charities, Epilepsy Action, Epilepsy Society and Young Epilepsy, with only minor adaptations used in order to compare data across different jurisdictions.

The survey results reported below are based on data from 404 respondents who completed the survey online between December 9th 2019 and February 28th 2020. Data from the following groups was excluded:

- Respondents <16 years' old
- Respondents outside the ROI
- Respondents who were not women/ girls taking valproate (on or after 1 August 2018) or the parent/ guardian/ carer of a girl taking valproate in that time.

The data below relates to the remaining cohort of 151 respondents.

78% were women taking valproate; 9% were parents/carers of a girl under 16 with epilepsy and 7% were a parent/carer of a woman with epilepsy who lacks mental capacity. Overall, 56% have been seizure-free for at least 12 months.

## Key Findings

### Awareness

- 83% of respondents were aware that taking valproate in pregnancy can, in some cases, cause serious birth defects.
- 66% of respondents were aware that taking valproate in pregnancy can, in some cases, cause learning and development problems in children.
- Only 27% of respondents said they had heard of the PPP, despite many of these women being aware of the risks of taking valproate during pregnancy and having received some of the programme materials.
- Just 30% of respondents said they had received a letter from the HSE informing them of the risks and asking them to contact their healthcare team to organise a review between July and October 2018. 45% said that they had not received this letter and 25% said they did not remember.

### Communications with Healthcare professionals

- Only 71% of respondents have ever had a discussion with a health professional about the risks of valproate in pregnancy
- Of the group who have ever had a discussion, 56% said that it took place since 1 August 2018. This represents just 39% of all respondents who have had a discussion since the introduction of the PPP.
- 67% of respondents said that they had met with their GP about their epilepsy since August 1 2018. Of these, 66% said that their GP had discussed the risk of valproate in pregnancy with them at that consultation. 34% reported that their GP did not discuss valproate risks.
- 62% of respondents said that they had met with an adult neurologist since August 1 2018. Of those, 77% said that the adult neurologist discussed the risks associated with taking valproate during pregnancy. 23% reported that the neurologist did not discuss the risks.
- 27% of respondents had met with a paediatric neurologist in that time. In 56% of cases, valproate risk was discussed, while in 44% of cases, it was not.
- 27% of respondents had met with an Epilepsy Nurse Specialist (ESN) after August 1 2018. 83% of those respondents said that their ESN had discussed valproate risks, while just 17% said the ESN had not.

### Patient Information Materials

- Just 30% of respondents said that they had received the Prevent: Patient Alert' card since August 1 2018 when receiving their prescription. 52% said they had not, while 18% could not remember.
- 30% also said that they had been given the 'Prevent: Patient Guide For Women & Girls' booklet and by their GP or another doctor or nurse. 51% said they had not been given the booklet and 22% could not remember.
- 75% of respondents said that they had received the patient information leaflet (PIL) with their prescriptions. 13% said they had not, while 12% said they could not remember.
- 14 of 128 respondents (11%) had not received ANY of the above materials.
- Of patients that received the materials, the feedback was positive:
    - 74% said that they fully understood the patient alert card; 23% said they partly understood it, while just 3% said they did not understand it.

- 79% said that they fully understood the booklet; 18% said they understood it partly and 3% said they did not understand it.

**Annual Risk Acknowledgement Form**

- 62% of respondents said they had not been asked to sign the Annual Risk Acknowledgement Form. 22% said that they had been asked, while 16% said they could not remember.

**Outcomes of consultations**

102 respondents answered the question on the outcome of their most recent discussion with their GP, neurologist or ESN.

- 23% of these were already taking valproate and were switched to another medicine.
- 10% were already taking valproate, decided to continue taking it and their doctor signed them up to the valproate pregnancy prevention programme
- 33% were already taking valproate, decided to continue taking it, but their doctor did not sign them up to the valproate pregnancy prevention programme
- 4 individuals (4%) reported that they were prescribed valproate for the first time but were not signed up to the valproate pregnancy prevention programme
- No respondents reported that they were prescribed valproate for the first time and were signed up to the valproate pregnancy prevention programme
- The reasons for starting or continuing valproate treatment were:
  - 48% - Not pregnant or planning a pregnancy
  - 34% - Healthcare professional advised valproate was the best drug for me
  - 49% - Other anti-epileptic drugs failed or caused side-effects
- Of those that started or continued valproate treatment, 21% said that they had to change their contraceptive method or start contraception in order to receive a prescription for valproate. The majority did not have any particular feelings about this – just 11% said they felt happy with this and 17% said they were unhappy.
- Of the 23 women who switched to a different AED:
  - The reason for switching for 3 women was that they were pregnant or planning a pregnancy. 15 women said they were not pregnant or planning a pregnancy but, after discussion of the risks, they decided to switch in case of future pregnancy.
  - 8 said that their seizure control was now better since the switch; 14 said there was no change, while one person reported that their seizure control was worse.
  - 20 are still on the new medication at the time of the survey. None have been switched back to valproate.
- The survey asked respondents to identify how they felt following their discussion with a health professional about risks. Of those who had the discussion, he most common answers were:
  - Better able to make a decision about my medication and my epilepsy (40%
  - Better Informed (32%)
  - Worried (25%)

- Uncomfortable (10%)
- Confused (8%)

**Valproate dispensing from the pharmacist**

- In relation to the most recent occasion respondents received valproate from their pharmacist, 72% said they received it in the manufacturer's original box with a patient alert card and/or booklet. 9% said it was in the manufacturer's original box but with they were not given a patient alert card or booklet. 4% said they received it in a plain box/ plastic bag with no alert card/ booklet or PIL.
- Of those that received valproate in a plastic bag or plain box, 31% said that it "always" has a warning pictogram sticker on the box. 25% said that this sticker is "never" present on the box.
- Just 12% of respondents said that their pharmacist "always" speaks to them about the risks associated with taking valproate during pregnancy when they collect their valproate prescription. 11% said that their pharmacist discusses it "more than half of the time"; 15% responded "less than half the time", while a majority, 54% said that their pharmacist "never" discusses the risks when they pick up their prescription.
- In terms of information provided by pharmacists:
  - 62% said that the pharmacist "always" provides the patient information booklet; 19% receive it some of the time; while just 11% said that they have "never" received the booklet from their pharmacist.
  - The patient alert card appears to be less frequently used by pharmacists. 10% said that it is "always" provided; 17% said that it is provided some of the time while 53% said that it was "never" provided.

**Satisfaction with the Prevent Programme**

Of 121 respondents who answered the survey's final question, "Overall, how satisfied are you that the Valproate Pregnancy Prevention Programme (Prevent) is fair for women with epilepsy?":

- 22% were very satisfied or satisfied
- 12% were unsatisfied or very unsatisfied
- 17% were not sure
- 48% said they did not know about the Prevent Programme.
- Looking only at those who had heard of it, 43% were satisfied/ very satisfied; 24% were unsatisfied and 33% were not sure.

## Summary & Conclusions

***Awareness has not changed significantly since 2016***

The survey clearly shows that there are women taking valproate who are still not aware of the associated risks. While 83% were aware of the risk of physical disabilities in children exposed in the womb (prior to taking the survey), just two-thirds were aware of the risks of developmental disabilities. Despite all of the efforts over the past two years by the State and patient organisations like Epilepsy Ireland and OACS Ireland, this does not represent a significant change from the previous EI survey in 2016 when 21% said they were not aware (Note: there was no distinction in that survey between physical and developmental disabilities). More work is needed to make sure that all women taking valproate are aware of the risks of taking it during pregnancy.

***Patients are not aware of the Prevent Programme and communication about risks still needs to be improved***

There are still too many women reporting that they have not had a discussion on valproate risk with a healthcare professional. 3 in 10 women say they have NEVER had a discussion about this with their healthcare team. There is also a general lack of awareness of the Prevent Programme itself - just over 1 in 4 women had heard of it. Even though the PPP requires annual risk monitoring with all women on valproate, just 4 in 10 have had a discussion since the introduction of the PPP, almost 18 months before the survey opened. Similarly, only about 4 in 10 women have been asked to sign the annual risk acknowledgement form in that time. Clearly, more needs to be done to explain the PPP to women taking valproate.

***Scope for improvement among GPs, neurologists and specialist nurses***

The data suggests that GPs in particular need to be more proactive in discussing valproate risks with their patients. 1 in 3 women who have met their GP about epilepsy since August 2018 say their GP has not discussed the risks. Neurologists also need to be more proactive – almost a quarter of women (who had an appointment since August 2018) report their neurologist did not discuss the risks. Specialist Nurses are more proactive on the issue, with over 4 in 5 women saying their nurse discussed risks with them.

Overall, these figures represent an improvement from 2016, when 44% of respondents said they had not had any conversations with their healthcare team (Note: that number was at almost 90% in our April 2015 survey). Nonetheless, the data suggests that we are some way off informing and educating ALL women on the drug.

The recruitment of four unfilled ESN posts and one consultant post as detailed in the HSE's Valproate Response Project report to the Department of Health in October 2019 is a critical component in achieving this and needs to be immediately addressed.

***Pharmacists too can help improve communication.***

Positives from the data include the percentage of women (72%) who receive their drug in the correct packaging with the booklet/ information card and the

utilisation by pharmacists of the patient booklet (just 11% said their pharmacist has never provided it). However, over half of respondents also said that their pharmacist has never spoken to them about valproate risks, while utilisation of the alert card is also comparatively poor.

***Discussing risk is generally positively received by patients***
For those that have had the conversation on risk, the most common feelings were 'better informed' and 'better able to make a decision'. While a significant number of women were also worried, the data highlights the need to ensure that ALL women taking valproate can be better informed and better able to make important decisions.

***Educational materials are underutilised but informative when used.***
The use of information materials including the patient alert card and the patient booklet appears to be sketchy, despite their availability in print and online format. For both, over half of all respondents said they had not received it from their GP/ Neurologist/ Nurse. 11% of women have not received any written materials. These shortcomings need urgent and immediate attention. More positively, women who received the information found that it clearly explained the risks. Another positive finding is that 3 in 4 women said they are receiving the package information leaflet (PIL) – this has historically been a major issue, largely as a result of broken bulk packaging while led to the drug being dispensed in plastic bags without critical safety information.

***Valproate use outside of the PPP appears to be common***
It is very concerning that despite the licencing conditions for valproate requiring a prescription only to be made after the Annual Risk Assessment form has been completed, a third of women who discussed risks with their health professionals reported that they have continued to be prescribed valproate, without being signed up to the PPP. This is three times more than the number of women who continue to take the drug under the PPP. Even more alarming is that 4 women in our survey were prescribed valproate for the first time, but weren't signed up to the PPP.

***HSE's mailshot to women and their GPs was only moderately successful.***
HSE's efforts in 2018 to contact all women on valproate by post appears to have been only moderately successful. Just 3 in 10 respondents said they had received the letter, with almost half saying they had not. Further methods of contacting women on valproate are required, especially in light of the significant minority who are still unaware of the risks.

***For those who have switched drugs, self-reported outcomes appear favourable***
Although based on very limited numbers (23) as well as a short timeframe, there were no switchbacks reported among those who were prescribed a different drug through the PPP, and almost all respondents said that seizure control was better or the same.

***There is a possibility of 'biased data'***
It must be acknowledged that this survey has a number of limitations. Firstly, it includes only self-reported survey data and there is no data collected from

clinical records. As it requested patients to answer questions based on a 16+ month timeframe, it is also potentially prone to significant recall bias. Finally, and perhaps most importantly, it is very likely that the majority of respondents had a prior relationship of some form with organisations like Epilepsy Ireland or OACS Ireland and would therefore be more likely to be aware of issues around sodium valproate. The extent of this factor is unknown but it is possible that a more population-representative sample would uncover even less favourable data in particular concerning levels of awareness.

As a result of these limitations, we suggest that this data should be read in conjunction with emerging RCSI/ HPRA data from health professionals in order to develop a full picture on the impact of the risk prevention measures in place since 2018.

***The issues are not unique to Ireland but UK data suggests we are lagging behind.***

UK charities Epilepsy Action, Epilepsy Society and Young Epilepsy have conducted a very similar survey of 500+ people with epilepsy in the UK. Findings from that survey are also set to be released in July 2020 and will be available from:
Epilepsy Action: www.epilepsy.org.uk
Epilepsy Society: www.epilepsysociety.org.uk
Young Epilepsy: www.youngepilepsy.org.uk

***There remains an urgent need for co-ordinated action***

While some progress has been made in recent years in minimising risks associated with valproate in pregnancy, it is clear that a number of significant concerns remain. The challenges outlined above can only be addressed by co-ordinated planning and action from a range of stakeholders. These stakeholders include the HSE, HPRA, Pharmaceutical Society of Ireland, Irish Pharmacy Union, ICGP and patient groups including Epilepsy Ireland and OACS Ireland. Epilepsy Ireland calls for the establishment of a stakeholder forum to consider all available data on this issue and to develop, implement & monitor new actions to address the identified issues.

## Appendix 1:
## Selection of quotes from respondents

"Since I changed GP, my new GP told me I was his only patient on sodium valproate. I saw my neurologist last week and is now changing to keppra"

"Was already on valproate, was aware of potential problem so sought contraception options with doctor to avoid pregnancy"

"The GP referred to this [PPP] in a telephone conversation however there has been no follow up which I'm not surprised about really!"

"Refuse to take anything else - other alternatives… screwed up my life. So Epilim is my only choice and neurologist appreciates my position"

"I continued to take Epilim Chrono and I am already taking a contraceptive pill. I understand the risks however being seizure free for more than 12 years I don't want to come off the medication"

"I decided to continue taking valproate as I want my seizures controlled"

"I have never been advised by [neurologist] about a pregnancy prevention programme. I was with [neurologist] every year and its only … this year he discussed about the side effects of sodium valproate when taken during pregnancy"

"Very angry as my neurologist knew I was trying for a child and referred me to a gynaecologist knowing the effects of valproate but never told me".

"This was not new information; I was made aware of the issues when I started taking Epilim 15 yrs. ago by my neurologist as any decent healthcare professional should have done. I was told in event of pregnancy that once the level of valproate didn't go above a certain amount I would be safe and we could monitor it. I suddenly then started to be bombarded with info and couldn't attend a GP without a lecture on taking Epilim regardless of whether that was what I was there about. It seems the HSE knew all along but suddenly decided it was no longer safe. My neurologist recommended changing because he said otherwise I'd never get a bit of peace going to the chemist or GP again . I had to stop driving for 3 months and luckily the new drug worked but I was never in the dark about these issues as I have an excellent neurologist and never had concerns whilst attending him that if I did become pregnant he would have taken any necessary precautions to look after both me and an unborn child"

"I didn't know what valproate was and that it was in the medication [I was taking]"

"Why is it called pregnancy prevention? That should NOT be the goal. The goal should be better communication between neurologist and patient so the patient can in fact try other medications".

"Since I was on a low dose on [multiple pregnancies] I was told it was very safe and to take folic acid 5mg to prevent spina bifida. My GP never sat me down to explain anything. When I rang my neurologist I was told it wasn't safe and got this booklet a few days later. Still confused as I was on a low dose"

"I think there are plenty of other medications and as this has a concern it shouldn't be prescribed to girls of any age".

"Found out about it too late after having 2 children and losing 2 children. Only ever knew about risks of spina bifida and took folic acid. Was never aware of developmental risks…"

"…Also, having been of childbearing age I couldn't understand why It was suggested in the first place before other possibilities"

"Why it was given AFTER my children were born, why all this information was not offered to me pre conception?"

[In relation to "Why did you want to stay on, or start taking, valproate?] – two 'other' responses include Vasectomy; Hysterectomy.