Supplementary Information

Spring - February 27th 2026

Regulatory Updates

1. Health Products Regulatory Authority (HPRA) Drug Safety Newsletter 121 published on December 22nd 2025 highlighted and reminded healthcare professionals of certain safety aspects regarding the use of Glucagon-like Peptide one (GLP-1) receptor agonists. One of their key message included a reminder GLP-1 analogues are not recommended for use during pregnancy.(1)
2. Direct healthcare professional communication (DHPC) from December 2025 alerted to important safety information from Pfizer regarding Tranexamic acid intravenous formulations, including the potential for serious, including fatal, adverse reactions due to inadvertent intrathecal administration.(1)
3. European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) provided an update on the European level evaluation of paternal exposure to valproate and the risk of neurodevelopmental disorders (NDDs) in offspring (detailed below).

December 2025

HPRA DRUG SAFETY NEWSLETTER

121ST EDITION

In this edition

- Fezolinetant: Risk of drug-induced liver injury and new recommendations on monitoring of liver function before and during treatment.
- Eosaltamide and digoxin: Laboratory test interference leading to falsely elevated digoxin plasma levels and a reminder of the existing interaction.
- Glucagon-like peptide-1 (GLP-1) analogues: Highlight and reminder of certain safety aspects.
- Product information updates for Macrogol 3350 with electrolytes (oral use), trimethoprim, and domperidone medicines.
- Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter.

Fezolinetant: Risk of drug-induced liver injury and new recommendations on monitoring of liver function before and during treatment

Key Messages

- **Serious liver injury** has been observed with fezolinetant (Veoza®).
- **Liver function tests (LFTs)**: LFTs must be performed prior to initiation of fezolinetant. Treatment with fezolinetant must not be initiated if serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) levels are ≥2x upper limit of normal (ULN) or if total bilirubin levels are ≥2x ULN.
- **Monitoring requirements**: During the first three months of treatment, monthly LFTs must be performed, and thereafter based on clinical judgement. LFTs must also be performed when symptoms suggestive of liver injury occur.
- **Treatment with fezolinetant must be discontinued if**:
  - Transaminase elevations are ≥3x ULN with: total bilirubin >2x ULN OR if patients develop symptoms of liver injury;
  - Transaminase elevations >5x ULN.
- **Continued monitoring**: Monitoring of LFTs should be maintained until normalisation.
- **Need for medical attention**: Patients must be advised to immediately seek medical attention if they experience signs or symptoms that may suggest liver injury such as fatigue, pruritus, jaundice, dark urine, pale faeces, nausea, vomiting, decreased appetite and/or abdominal pain.

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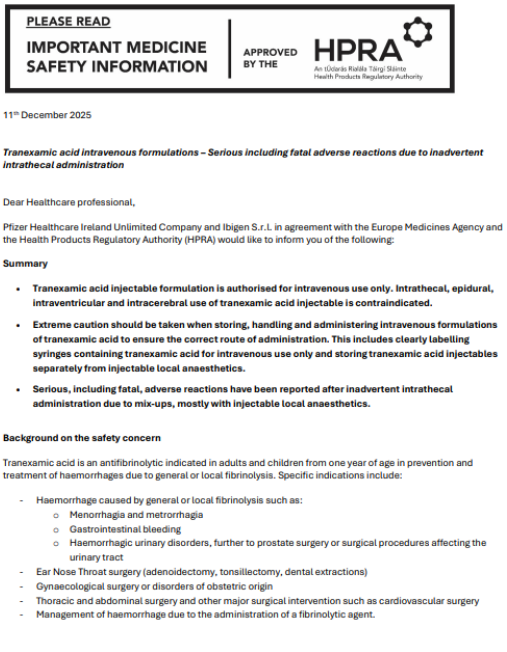


PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

11th December 2025

Tranexamic acid intravenous formulations – Serious including fatal adverse reactions due to inadvertent intrathecal administration

Dear Healthcare professional,

Pfizer Healthcare Ireland Unlimited Company and Ibigen S.r.l. in agreement with the Europe Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- **Tranexamic acid injectable formulation is authorised for intravenous use only. Intrathecal, epidural, intraventricular and intracerebral use of tranexamic acid injectable is contraindicated.**
- **Extreme caution should be taken when storing, handling and administering intravenous formulations of tranexamic acid to ensure the correct route of administration. This includes clearly labelling syringes containing tranexamic acid for intravenous use only and storing tranexamic acid injectables separately from injectable local anaesthetics.**
- **Serious, including fatal, adverse reactions have been reported after inadvertent intrathecal administration due to mix-ups, mostly with injectable local anaesthetics.**

Background on the safety concern

Tranexamic acid is an antifibrinolytic indicated in adults and children from one year of age in prevention and treatment of haemorrhages due to general or local fibrinolysis. Specific indications include:

- Haemorrhage caused by general or local fibrinolysis such as:
  - Menorrhagia and metrorrhagia
  - Gastrointestinal bleeding
  - Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract
- Ear Nose Throat surgery (adenoidectomy, tonsillectomy, dental extractions)
- Gynaecological surgery or disorders of obstetric origin
- Thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery
- Management of haemorrhage due to the administration of a fibrinolytic agent.

(1)

Paternal Valproate Use

Since April 2024, new precautionary measures have been in place regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months prior to conception.

This followed a post authorisation safety study (PASS) conducted by the companies that market valproate-containing medicines in the EU. Data analysis was from multiple registry databases in Denmark, Norway and Sweden. At the time of assessment, the European Medicines Agency (EMA) safety committee, known as the Pharmacovigilance Risk Assessment Committee (PRAC), recognised certain limitations of the PASS data. However, together with other available information they concluded, NDD's may pose a potential risk in children conceived by men treated with valproate within three months prior to conception.(2)

New data has emerged in the past year including that from a study analysing multiple databases in Denmark. This study investigated the potential risk of NDD's in children born to men treated with valproate, levetiracetam or lamotrigine before conception and did not suggest an association between valproate use by the father and an increased risk of NDD in the child.(3)

PRAC has since initiated a signal procedure to assess and validate the potential risks. In doing so, they are currently reviewing the data to understand the differences in findings across the studies. Included in their review is a paper which assessed genetic susceptibility to epilepsy, ADHD and autism spectrum disorders (ASD) in fathers with epilepsy treated with valproate, lamotrigine or levetiracetam, other anti-seizure medications. This paper suggested genetic factors may confound studies of paternal ASM use and neurodevelopmental outcomes in children.(4)

Commentary from the European Teratology Information Service (ENTIS) and Organisation of Teratology Information Specialists (OTIS) gives the opinion that warnings from the European Medicines Agency (EMA) and the Medicines and Healthcare Regulatory Authority in the UK, were premature and that the underlying scientific data do not convincingly substantiate the inference of a paternally mediated risk from valproate to children.(5) Nonetheless, current recommendations remain regarding precautionary measures for the treatment of male patients with valproate medicines. These can be found on the HPRA website here.(6)

(6)

Figure 1: *Information resources for male patients using valproate containing medicines.*

Paracetamol exposure during Pregnancy and Child Neurodevelopment

A global public debate was sparked in September 2025 when the US Food and Drug Administration (FDA) suggested prenatal exposure to paracetamol may be associated with an increased risk of neurological conditions such as autism and Attention Deficit Hyperactivity Disorder (ADHD) This was based on studies that linked paracetamol use in pregnancy to neurodevelopmental outcomes, which were characterised by methodological limitations including by variability and significant differences in how studies defined exposure and outcomes.(7,8)

A systematic review and meta-analysis titled 'Prenatal paracetamol exposure and child neurodevelopment' was published The Lancet Obstetrics, Gynaecology & Women's Health in January 2026.(9) This study did not indicate a clinically significant increase in the likelihood of Autism Spectrum Disorder (ASD), ADHD or intellectual disability in children of pregnant individuals who used paracetamol as directed. The results are strengthened by the fact that the authors looked at studies with rigorous study design (large sibling-comparison cohorts) and those rated highest for methodological quality.

The authors followed a pre-specified, registered protocol and conducted a robust analysis of all relevant high-quality studies on this topic. This was an unfunded study and the authors reported no conflicts of interest. In total, 43 studies were reviewed, and 17 were included in the combined meta-analysis. One of the studies, a Swedish cohort study, included 2.48 million births and found no association with NDD when accounting for familial cofounding.

Paracetamol is the medication of choice in pregnancy for pain and fever as it doesn't carry the risks associated with other analgesia like ibuprofen or oxycodone. Unnecessarily avoiding paracetamol could lead to risks from untreated fever or severe pain leading to adverse pregnancy outcomes. Given paracetamol is the most widely used medicine to treat pain and fever during pregnancy, this robust review provides reassurance for the public and health professionals.

The review provides strong evidence that supports existing recommendations to endorse the safe use of paracetamol during pregnancy when used appropriately. The findings align with position statements from multiple medical organisations including the American College of Obstetricians & Gynaecologists, the Royal College of Obstetricians & Gynaecologists, the European Network of Teratology Information Services, the HPRA and other international medication regulators.(9)

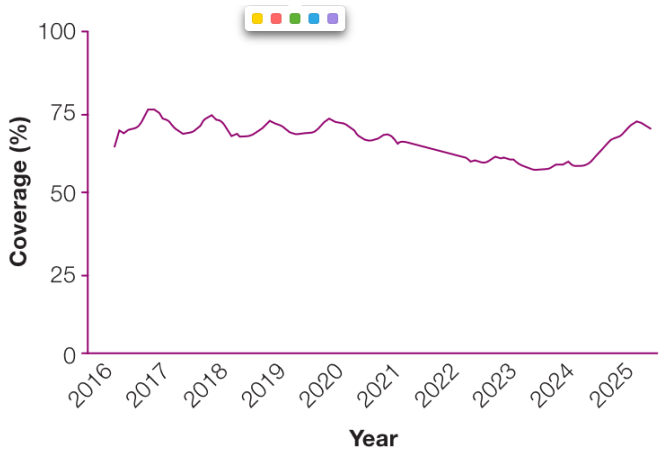
Trends in Practice

1. Pertussis Vaccination Rates – An Update from the UK Health Security Agency (UKHSA)

Maternal vaccination against pertussis infection, commonly known as whopping cough, is very effective at protecting young babies against serious complications of pertussis infection. Such complications can include respiratory distress, hospitalisation and in some cases death. In Ireland, the Health Protection Surveillance Centre (HPSC) reported record high number of cases of pertussis in 2024 with trends continuing to rise in 2025.(10) In March 2025, the Health Service Executive issued a reminder for pregnant women to avail of the whooping cough vaccine that is free of charge from participating GP's.

The whooping cough vaccine is offered to all pregnant women usually at a woman's 20 week scan. It can be given from week 16 and ideally by 32 weeks of pregnancy for optimal protection. It can be given later than 32 weeks if not given earlier in pregnancy. Evidence from England shows that vaccination at the right time in pregnancy is highly effective, providing 91% protection against infant death with whooping cough.(11,12)

Data on the uptake of whooping cough vaccines among pregnant women in Ireland is not routinely available. However, an update from the UK Health Security Agency (UKHSA) in December 2025 reported over 72% of pregnant women who gave birth in September 2025 were vaccinated against whooping cough, up from 64% last year and 58% in 2023.(11,12)



(11)

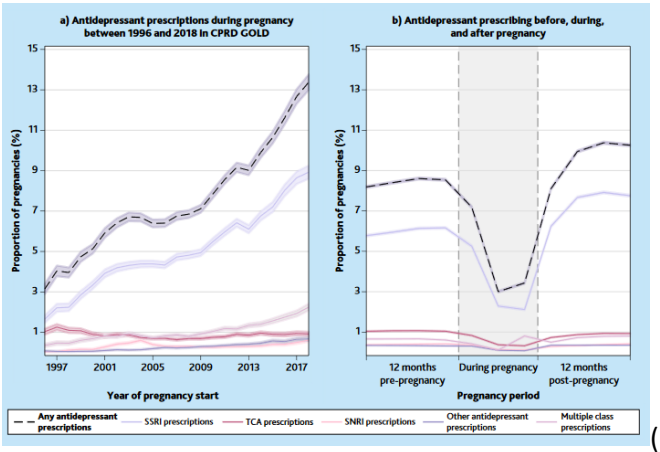
Figure 2: *Monthly pertussis vaccination coverage (%) in pregnant women in the UK from April 2016 to June 2025.*

2. Patterns of antidepressant prescribing around pregnancy

The use of antidepressants in pregnancy involves a careful risk benefit assessment that balances maternal mental health with the potential harms to the foetus. While it is known antidepressant use during pregnancy is increasing, a recent study using primary care data from the UK gives further insights into the prevalence and patterns of antidepressant prescribing in pregnancy.

This group analysed primary care prescription records to identify individuals who had been prescribed antidepressants in the perinatal period between 1996 and 2018. They compared patients who were prescribed anti-depressants before and during pregnancy with those newly prescribed anti-depressants during pregnancy. They also investigated post pregnancy exposure and characteristics associated with anti-depressant discontinuation at any time during pregnancy.(13)

From their results, 79,144/1,033,783 (7.7%) individuals were prescribed antidepressants during pregnancy and 15,733/79,144 (19.9%) were newly prescribed antidepressants during pregnancy. Antidepressant prescribing during pregnancy increased from 3.2% (556/17,653) in 1996 to 13.4% (3889/29,079) in 2018. Most women in both groups discontinued their medication at some point during pregnancy. Over half of those who discontinued during pregnancy were prescribed antidepressants in the 12 months after pregnancy (53.0%, 23,457/44,228). They also found younger age, previous stillbirth and high deprivation were associated with more frequent discontinuation anytime during pregnancy.(13)



(13)

Figure 3: *(a) Antidepressant prescribing during pregnancy over time in Clinical Practice Research Datalink (CPRD) GOLD. (b) Proportion of pregnancies in individuals who were prescribed antidepressants before, during, and after pregnancy.*

According to new research presented at the Society for Maternal-Foetal Medicine (SMFM) 2026 Pregnancy Meeting in February, women who stop taking antidepressants during pregnancy are almost twice as likely to have a mental health emergency as those who continue treatment. This group of researchers from the Hospital of the University of Pennsylvania, Philadelphia looked at data from almost 4,000 women who gave birth between January 2023 and December 2024 and were prescribed a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) in the three months prior to becoming pregnant.(14)

The results showed that women who stopped their medication, or had gaps of more than 60 days between prescriptions, were more likely to experience serious mental health issues. They were also significantly more likely to experience a mental health emergency during pregnancy compared with women who continued to take their medication throughout their pregnancy. The highest risks were in the first (58/1,000 vs. 37/1,000, p=0.02) and ninth months of pregnancy (59/1,000 vs. 29/1,000, p<0.01).(14–16)

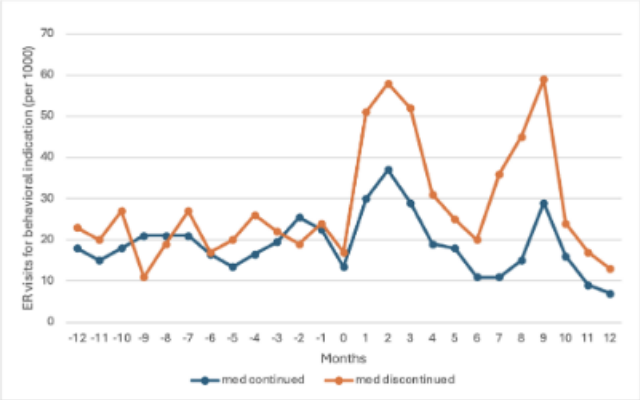


Figure 4*.Rates of mental health emergencies amongst patients who continued vs. discontinued antidepressants in pregnancy. (Jan 1st, 2023 - Dec 31st, 2024).(14)*

While it is generally accepted antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs) are appropriate to use and often necessary in pregnancy, inconsistencies in information communicated to women remains. In July of 2025, an FDA expert panel discussion on 'Selective Serotonin Reuptake Inhibitors (SSRIs) and Pregnancy' raised concerns over congenital malformations, autism, and developmental issues with the use of SSRI's in pregnancy.(17) Despite this, many professional medical groups, including the American College of Obstetrics and Gynaecologists (ACOG), continue to support the safe and necessary use of SSRIs in pregnancy.(18)

In summary, prescribing rates of antidepressant during pregnancy are increasing and patterns of discontinuation as well as resumption in the postnatal period are common. The decision to continue or discontinue antidepressants during pregnancy should be based on a shared decision-making process that considers the risks and benefits to both the mother and infant. Hence, counselling women of childbearing age when initiating antidepressants, as well if and when they become pregnant, is key to supporting and empowering informed decision making.

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