Valproate ▼(Epilim, Depakote, Convulex, Episenta, Epival, Sodium Valproate, Syonell, Belvo & Dyzantil)

Contraception and Pregnancy Prevention – Important information to know.

- Valproate is an effective medicine for epilepsy and bipolar disorder.
- Valproate can seriously harm an unborn baby when taken during pregnancy and may lead to permanent disability.
- Use an effective method of birth control (contraception) at all times during your treatment with valproate.
- It is important to discuss and review your treatment with a specialist at least once each year.

▼ These medicines are subject to additional monitoring. Report any side effects to **www.mhra.gov.uk/yellowcard** or search for MHRA Yellow Card in the Google Play or Apple App Store.

Keep this card safe so you always know what to do.

WARNING FOR WOMEN WHO ARE ABLE TO BECOME PREGNANT

- This medicine can seriously harm an unborn child.
- Always use highly effective contraception during your treatment with Topiramate.
- If you become pregnant, talk to your doctor straight away.
- If you have epilepsy, do not stop taking this medicine unless your doctor tells you to.

Please read the Package Leaflet, Patient Guide and Patient Card for further information
Date of Approval: 31 May 2024

NHS
South East London

Valproate & Topiramate

Implementation of the National Patient Safety Alert/Drug Safety Update

Valproate

NHS
South East London

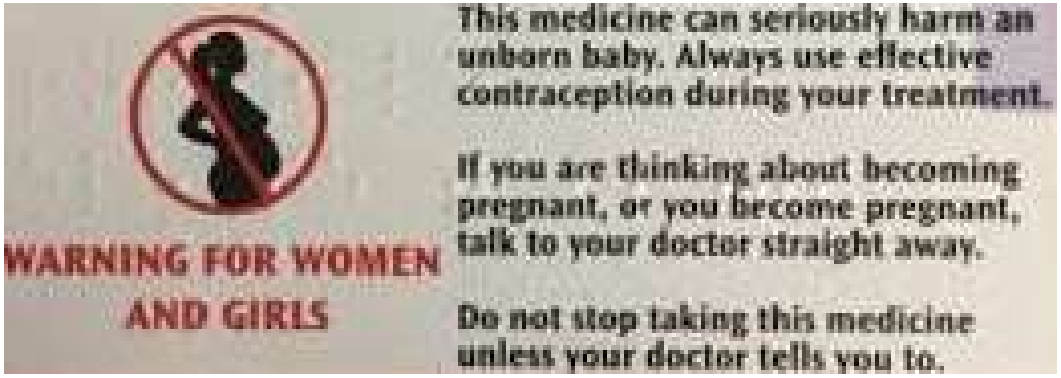
Valproate - sodium valproate, valproic acid and valproate (Epilim, Depakote and other generic brands)

Valproate is an **effective treatment** for epilepsy, bipolar disorders and prescribed off-label for a range of conditions.

Valproate has a **high teratogenic potential**, and children exposed in utero to valproate have a high risk for **congenital malformations** (11%) and **neurodevelopmental disorders** (up to 30- 40%) which may lead to permanent disability.

High risk medicine with a range of indications:

- Epilepsy
- Bipolar disorder management
- Unlicensed indications (off-label uses)
  - Migraine prophylaxis
  - Neuropathic pain
  - Dementia
  - Depression



Valproate – PREVENT (PPP)

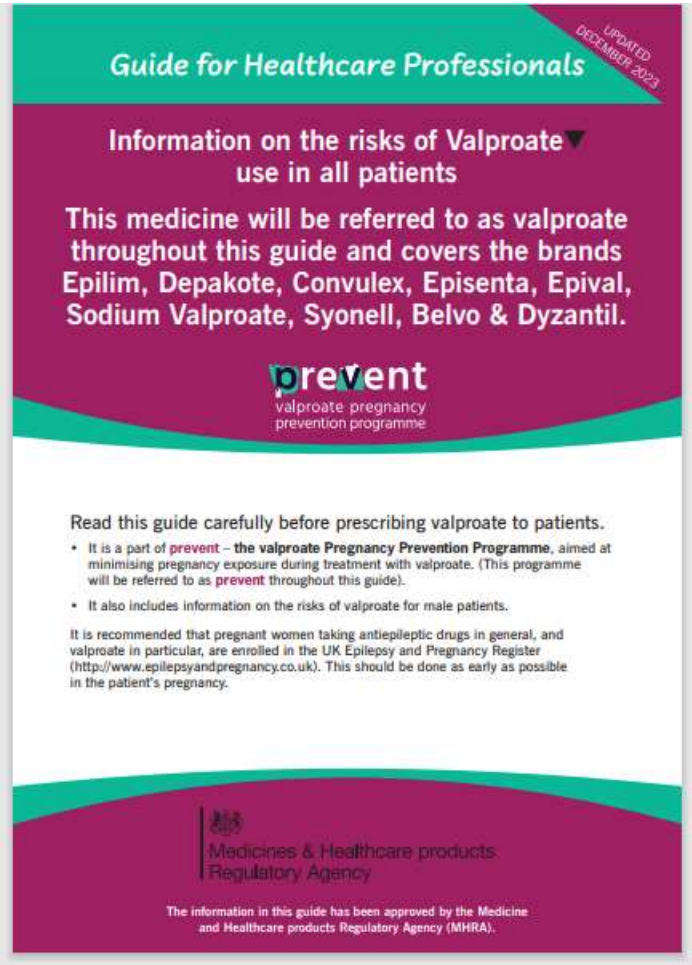
NHS South East London

Valproate - sodium valproate, valproic acid and valproate semisodium

- Associated with a **significant risk** of **birth defects** and **developmental disorders** in children born to women who take valproate during pregnancy.

- Since 2018 any use of valproate in patients of **childbearing potential** must be within the terms of the **Pregnancy Prevention Programme (PREVENT)**.
- This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant.

https://www.medicines.org.uk/emc/rmm/1203/Document



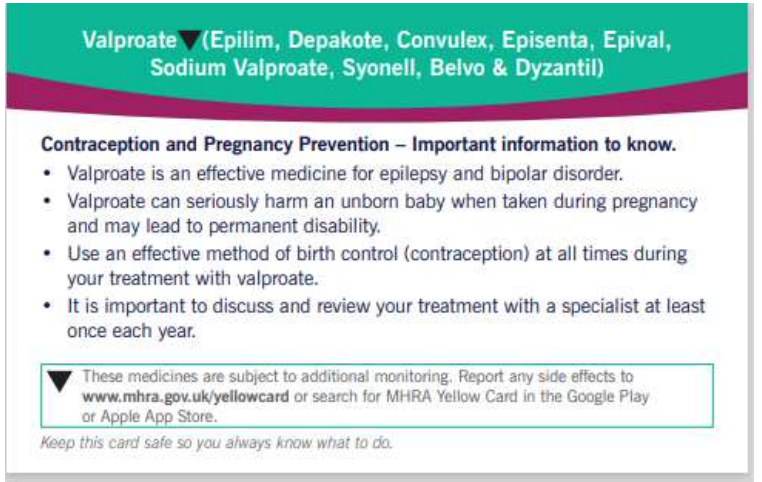
Valproate – PREVENT (PPP)

NHS South East London

Healthcare professionals who seek to prescribe or dispense valproate to their female patients must make sure this is within the terms of the PPP. **This includes the completion of a signed risk acknowledgement form when their treatment is reviewed by a specialist, at least annually.**

- These regulatory changes are further supported by:
  - smaller pack sizes to encourage monthly prescribing
  - a pictogram/warning image on valproate labelling
  - rules introduced in 2023 to ensure all patients receive the whole pack of valproate with the warnings on the box

[Valproate use by women and girls - GOV.UK (www.gov.uk)]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Contraception and Pregnancy Prevention – Important information to know.

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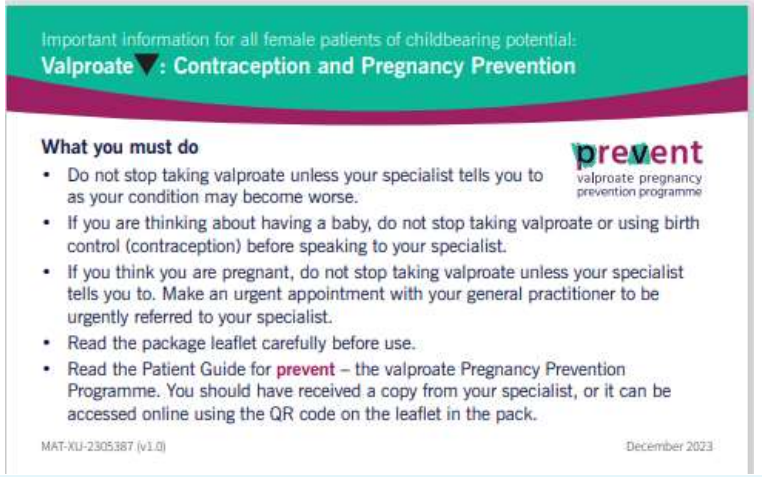
▼ These medicines are subject to additional monitoring. Report any side effects to **www.mhra.gov.uk/yellowcard** or search for MHRA Yellow Card in the Google Play or Apple App Store.

Keep this card safe so you always know what to do.


Important information for all female patients of childbearing potential:

Valproate▼: Contraception and Pregnancy Prevention

What you must do

prevent valproate pregnancy prevention programme

- Do not stop taking valproate unless your specialist tells you to as your condition may become worse.
- If you are thinking about having a baby, do not stop taking valproate or using birth control (contraception) before speaking to your specialist.
- If you think you are pregnant, do not stop taking valproate unless your specialist tells you to. Make an urgent appointment with your general practitioner to be urgently referred to your specialist.
- Read the package leaflet carefully before use.
- Read the Patient Guide for **prevent** – the valproate Pregnancy Prevention Programme. You should have received a copy from your specialist, or it can be accessed online using the QR code on the leaflet in the pack.

MAT-XU-2305387 (v1.0) December 2023


National Patient Safety Alert

Medicines & Healthcare products Regulatory Agency

Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients

Date of Issue:	28 November 2023	Reference No:	NatPSA/2023/013/MHRA

This alert is for action by: Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland)

This is a safety critical and complex National Patient Safety Alert. Implementation should be coordinated by an executive lead for quality (or equivalent) in Integrated Care Boards in England, Health Boards in Scotland, Health Boards in Wales, and Health and Social Care Trusts in Northern Ireland, alongside the Chief Pharmacist (or equivalent) and supported by the Medical Directors of organisations involved in the prescribing of valproate and clinical leads in neurology, psychiatry, paediatrics, learning disability and/or autism, contraception and sexual health, and general practice, with others included to meet local needs and clinical situations.

Explanation of identified safety issue:

The MHRA is asking organisations to put a plan in place to implement **new regulatory measures** for sodium valproate, valproic acid and valproate semisodium (valproate). This follows a comprehensive review of safety data, advice from the Commission on Human Medicines and an expert group, and liaison with clinicians and organisations.

Actions required

When: To begin as soon as possible and be completed by **31 January 2024**

1. Designate a new or existing group to co-ordinate the implementation of the new regulatory measures in providers, with oversight from a senior quality group. This group should include (but is not restricted to):

Valproate – What's new?

NHS South East London

November 2023

- MHRA issued a National Patient Safety Alert - NatPSA_2023_013_MHRA
- System wide approach to ensure valproate safety implementation across all organisations in SEL

Regulatory Changes – January 2024 (Oral Valproate)

- **A**. Valproate must not be started in new patients (male or female) younger than 55 years, unless **two specialists independently** consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply.
- **B**. At their **next annual specialist review**, women of childbearing potential and girls should be reviewed using a **revised valproate Risk Acknowledgement Form**, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes.
- Healthcare professionals should:
  - Continue to prescribe valproate and advise individuals of current risks.
  - **review the new measures and materials and integrate them into their clinical practice** when referring patients and when prescribing or dispensing valproate.

Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age - GOV.UK (www.gov.uk)

Valproate – What's new?

NHS South East London

5 September 2024 – Drug Safety Update in Men

- Valproate use in men: as a precaution, men and their partners should use effective contraception
- Possible association between valproate use by men around the time of conception and an **increased risk of neurodevelopmental disorders** in their children.
- Inform male patients who may father children of this possible increased risk and the recommendation to **use effective contraception** during valproate treatment and for at least 3 months after stopping valproate
- Valproate use in men: as a precaution, men and their partners should use effective contraception - GOV.UK (www.gov.uk)

Effective Contraceptives

- Men and women whose sexual partners are using valproate should use **effective contraception** *(condoms and another form of female contraception)* during use of valproate and for 3 months after the male partner stops valproate.
- If there is no pregnancy risk or if the woman is already using **highly effective contraception**, then condom use is not required to prevent pregnancy.
- **Highly effective -** male and female sterilisation, long-acting reversible contraceptives (LARC) - copper intra-uterine device (Cu-IUD), levonorgestrel intra-uterine device (LNG-IUD) and progestogen-only implant (IMP). (Avoid interacting drugs with females on IMP)
- Contraceptives, non-hormonal | Treatment summaries | BNF | NICE

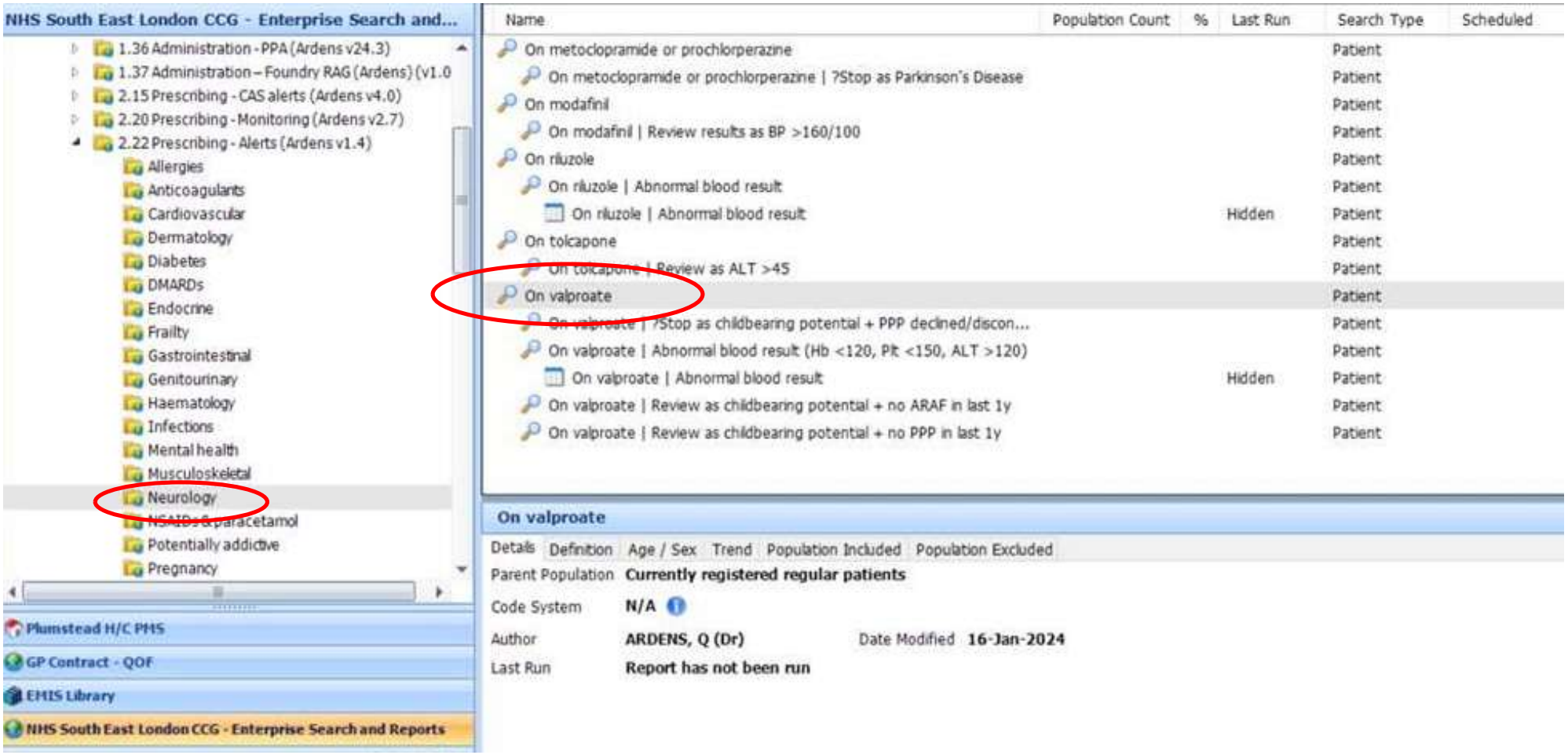
Valproate Safety

NHS
South East London

Healthcare professionals have a key role in ensuring valproate safely...

- Valproate must not be used in any woman or girl able to have children unless there is a **pregnancy prevention programme** (PPP) in place.
- Valproate must always be **dispensed in the manufacturer's original full pack** unless there are exceptional circumstance.
- Valproate must not be started in **new patients** (male or female) younger than 55 years, unless **two specialists independently** consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply.
- At their next annual specialist review, women of childbearing potential and girls should be reviewed using a revised **valproate Risk Acknowledgement Form**, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes
- **ACTION – Conduct Ardens search and ensure appropriate actions are taken then coded accordingly**

Valproate Safety – Arden Search on Emis



Valproate Safety – for General Practices

107995_Valproate_HCP_Booklet_DR15_v07_DS_07-01-2021.pdf (publishing.service.gov.uk)

South East London

NEW MALE STARTER:

1. Refer any new patient to a specialist prescriber for diagnosis and initiation of treatment (Specialist should discuss alternative treatment options, Valproate should only be started when two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of prevent are fulfilled .
2. Discuss the risk of infertility and the potential risk of testicular toxicity.
3. Ensure the patient has the Patient guide and a copy of the signed Risk Acknowledgement Form for male patients starting valproate is filed in the patient's medical records.
4. Remind all males patients a review at least annually should be in place whilst taking valproate

NEW FEMALE STARTER:

1. Refer any new patient to a specialist prescriber for diagnosis and initiation of treatment (Specialist should discuss alternative treatment options, Valproate should only be started when two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of prevent are fulfilled .
2. Discuss the need for patient to follow the requirements of **PREVENT** and the risk associated with taking teratogenic drugs during pregnancy
3. Exclude pregnancy by means of a negative pregnancy test
4. Discuss the need of Highly effective contraception
5. Ensure the patient has a copy of Patient guide and a copy of the signed Annual Risk Acknowledgement Form is filed in the patient's medical records.
6. Remind all female patients that they will need to see their specialist prescriber at least annually whilst taking valproate and arrange the referral annually as required.

EXISITING FEMALE PATIENTS:

1. Invite women and girls of childbearing potential for a review
2. Discuss the need for the patient to follow the requirements of **PREVENT**
3. Ensure the patient has the Patient guide and a copy of the signed Annual Risk Acknowledgement Form is filed in the patient's medical records.
4. Remind all female patients that they will need to see their specialist prescriber at least annually whilst taking valproate and arrange the referral annually as required.

Female patients who are PLANNING to become pregnant:

- Inform the patient not to stop contraception or valproate until told to by their specialist prescriber.
- Refer the patient to their specialist prescriber who is managing their condition.

Female patients who are PREGNANT:

- Inform the patient not to stop valproate and explain the reasons (e.g., their condition may become worse).
- Refer the patient to their specialist prescriber and ask for them to be seen urgently (within days)

Valproate Safety – for Community Pharmacies

[107995_Valproate_HCP_Booklet_DR15_v07_DS_07-01-2021.pdf (publishing.service.gov.uk)]

South East London Integrated Care System

Whenever you dispense valproate to any female patient:

1. Ensure the Patient Card is provided every time valproate is dispensed to a female patient.
2. Ensure the patient has received the Patient Guide or knows they can access it online using the QR code on the package leaflet.
3. Confirm with female patients that they have been made aware of the risks in pregnancy.
4. Confirm with female patients that they have been made aware to always use effective contraception and to see their General Practitioner (GP) to be urgently referred to their specialist, should they be planning a pregnancy.
5. Confirm with female patients that they have been made aware to **NOT TO STOP** valproate and to immediately contact their GP for an urgent referral to their specialist in case of suspected pregnancy.
6. Dispense valproate in the original package.
7. In exceptional circumstances, where a patient needs to receive their medication in different packaging such as a Monitored Dosage System, ALWAYS provide a copy of the package leaflet, the patient card and add a valproate warning sticker to the outer box.
8. If a female patient reports that:

   - They are not continuously taking an effective method of contraception,
   - They are not aware of the need for contraception or
   - They have not been seen by their specialist in the past year

   dispense their medicine and refer them to their GP (contact the GP if necessary).

prevent
valproate pregnancy prevention programme

Topiramate

NHS South East London

GOV.UK

Home > Drug Safety Update

Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme

Topiramate is now contraindicated in pregnancy and in women of childbearing potential unless the conditions of a Pregnancy Prevention Programme are fulfilled. This follows a review by the MHRA which concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child. Harms included a higher risk of congenital malformation, low birth weight and a potential increased risk of intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder in children of mothers taking topiramate during pregnancy.

From: Medicines and Healthcare products Regulatory Agency
Published 20 June 2024

Topiramate – Pregnancy Prevention Programme (PPP)

NHS South East London

Regulatory Changes – June 2024

- A recent review suggests an increased risk of **birth defects** and **low birth weight**, and a potential increased risk of **autism spectrum disorder**, intellectual disability and attention deficit hyperactivity disorder (ADHD) if topiramate is used in pregnancy.
- Because of these increased risks, topiramate should not be used:
  - In pregnancy for prophylaxis of migraine.
  - In pregnancy for epilepsy unless there is no suitable alternative treatment.
- Topiramate should not be used in patients of childbearing potential unless the conditions of the PPP are fulfilled.
- The PPP aims to ensure that for patients who are able to get pregnant:
  - Pregnancy is excluded before starting topiramate.
  - They are aware of the risks of topiramate use during pregnancy and the need to adhere to the PPP.
  - They understand the need to use highly effective contraception throughout treatment with topiramate and for at least 4 weeks after the last dose of topiramate.
  - Topiramate treatment is subject to regular, at least annual, review.

Topiramate

NHS South East London

MHRA launched the Pregnancy Prevention Programme (PPP) for Topiramate – June 2024

- A **regulatory action** from MHRA
- There are **no changes to the clinical indications** for Topiramate and it is not expected that NICE guidelines will change other than to reflect the introduction of the PPP.
- There is **no prescribed timeline** for prescribers to contact the prevalent population

High risk medicine with a range of indications:

- Epilepsy
- Migraine prophylaxis
- Unlicensed indications (off-label)
  - Mental health conditions
  - Neuropathic pain

Risk Awareness Forms:

- Epilepsy
  - Completion by specialist
  - GP team to ensure appropriately coded on the system
- Migraine prophylaxis
  - Completion by GP
  - Ardens search template to identify patient group then review and code on GP system

Topamax 25 mg Tablets - Risk Management Materials - (emc) (medicines.org.uk)

Conduct Ardens search, refer for specialist indications

Advice for prescribers:

- all women of childbearing potential being treated with topiramate-containing medicines must follow the requirements of the Pregnancy Prevention Programme. These conditions are also applicable to female patients who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy
- for all new women of childbearing, potential prescribers must:
  1. assess their potential for pregnancy and discuss the need for them to be on the Pregnancy Prevention Programme
  2. ensure that pregnancy has been excluded, by means of a negative pregnancy test, prior to starting treatment with topiramate
  3. inform them of the potential risks of topiramate use in pregnancy and counsel them on treatment options
  4. discuss with them the need to use highly effective contraception throughout treatment and for at least four weeks after the last dose of topiramate. See guidance from Faculty of Family Planning and Sexual Health on potential drug interactions with hormonal contraceptives and what this means for topiramate
  5. complete the Risk Awareness Form with the patient (or responsible person)
  6. provide a copy of the Patient Guide to the patient (or responsible person)
- for existing patients, prescribers must:
  1. identify all women and girls of childbearing potential on topiramate and invite them in for review
  2. complete the Risk Awareness Form with the patient (or responsible person) and at each annual review
  3. provide a copy of the Patient Guide to the patient (or responsible person)

Topiramate

NHS
South East London

Action – Conduct Ardens search and review / refer individuals based on the recommendations.

Materials to support the Pregnancy Prevention Programme:

Patient Guide for Migraine and Epilepsy - to be provided to all girls and women of childbearing potential who are started on, or continue to use, topiramate-containing medicines

Guide for Healthcare Professionals for Migraine and Epilepsy

Risk Awareness Form for Migraine and Epilepsy - for the healthcare professional and the patient (or responsible person) to sign at initiation of treatment with topiramate and at annual treatment reviews.

The patient should receive a copy of this form, a copy should be filed in the patient's medical notes, and, if necessary, a copy sent to the patient's GP

South East London
Integrated Care System

Thank you
Any Questions?