FSRH CEU Statement: New manufacturer/ MHRA advice regarding nomegestrol acetate – how does this affect prescribing of Zoely®?
13 April 2023

In response to evidence indicating an association between higher cumulative doses of nomegestrol acetate (NOMAC) and increased risk of intracranial meningioma, Theramex (in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA)), has issued a direct healthcare professional communications (DHPC) letter relating to prescribing of Zoely® (a combined oral contraceptive containing estradiol in combination with 2.5mg of the progestogen NOMAC).

The evidence does not relate directly to use of Zoely, but to use of preparations containing NOMAC at higher doses than in Zoely (3.75mg-5mg).

Background

Meningioma is uncommon. Incidence increases significantly with age: the European Medicines Agency (EMA) cites annual meningioma incidence of 1.44 per 100,000 people at age 20-34 years, 5.4 per 100,000 at age 35-44 years and 10.2 per 100,000 at age 45-54 years based on figures from a study in the USA.[1] Meningioma occurs more than twice as frequently in women than in men.

Nomegestrol acetate (NOMAC) is a potent progestogen with some antiandrogenic activity. In the UK, NOMAC is available only as the progestogen component of an estradiol-containing combined oral contraceptive, Zoely®, at the lower dose of 2.5mg daily. Pharmacovigilance in Europe - where NOMAC has been used as monotherapy at higher oral doses (eg. 5mg twice daily cyclically) for management of gynaecological conditions, and at a dose of 3.75mg as the progestogen component of combined hormone replacement therapy - identified a possible association between use of NOMAC and risk of intracranial meningioma.

Study evidence

NOMAC and risk of intracranial meningioma. A retrospective study[2] examined observational data from the French National Health Data System to inform incidence of meningioma amongst women who started use of NOMAC monotherapy (3.75mg or 5mg doses) between 2007 and 2018. The cohort did not include users of Zoely, and individuals with a prior diagnosis of meningioma or type 2 neurofibromatosis were excluded. The study compared incidence of intracranial meningioma in individuals exposed to higher cumulative doses of NOMAC (≥150mg over 6 months) with those exposed to very low doses (<150mg over 6 months). Compared with exposure to only very low doses of NOMAC the study reported significantly increased risk of intracranial meningioma with cumulative NOMAC exposure of 1.2g to 3.6g (adjusted hazard ratio (aHR) 2.6 (1.8-3.8). For cumulative NOMAC exposure of 3.6g to 6g and >6g, aHR was 4.2 (2.7-6.6) and 12.0 (8.8-16.5) respectively. Meningioma risk reduced to close to baseline within a year after cessation of NOMAC.

There are no data specific to meningioma risk with lower dose NOMAC preparations like Zoely, but with prolonged use of Zoely, cumulative NOMAC exposure could be high. An individual using Zoely as a 24/4 regimen would use a total of 1.2g of NOMAC over the course of about 18 months (although in combination with estradiol rather than as monotherapy).

Other progestogens and risk of intracranial meningioma. Use of cyproterone acetate at higher doses also has a known association with meningioma (see 2020 FSRH guidance on implications for prescribing of combined ethinylestradiol 35mcg / cyproterone acetate 2mg here[3]) There are not published studies to inform effect of other progestogens on risk of meningioma (except chlormadinone acetate which is not used in the UK). Pharmacovigilance does not appear, however, to have flagged concern about meningioma risk with other contraceptive progestogens.

Use of NOMAC after a diagnosis of meningioma. This study does not consider health outcomes when NOMAC is used by individuals who already have a diagnosis of intracranial meningioma. Very limited evidence from case reports identified by literature review carried out by the EMA suggested that meningioma might regress or stabilise after NOMAC is discontinued.[4]

FSRH CEU guidance

In line with MHRA/EMA guidance, FSRH CEU advises that Zoely should not be used by individuals who have or have had meningioma.

Additionally, although this evidence does not relate directly to Zoely, but to preparations containing higher doses of NOMAC, FSRH CEU suggests that:-

- Providers should advise users of Zoely that it is possible that higher cumulative NOMAC exposure resulting from prolonged use could increase risk of intracranial meningioma - although absolute risk would remain small.
- Any associated increase in meningioma risk would be expected to reduce towards baseline after stopping Zoely (as it does after cessation of higher NOMAC doses).
- Providers should be vigilant for symptoms and signs of meningioma in users of Zoely.
- Although absolute risk of intracranial meningioma remains low amongst NOMAC users, providers may wish to consider offering alternative effective contraceptive options, bearing in mind also that incidence of meningioma increases markedly with age.

Suspected adverse drug reactions should be reported to the MHRA through the Yellow Card Scheme.

The DHPC letter from Theramex Ireland Ltd, agreed with the Medicines and Healthcare products Regulatory Agency (MHRA) is available here.[5]

References

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