

**From the Chief Medical Officer
Professor Sir Michael McBride**



HSS(MD) 34/2023

FOR ACTION

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Dear Colleague

**MHRA DRUG SAFETY UPDATE: NON-STEROIDAL ANTI-INFLAMMATORY
DRUGS (NSAIDS): POTENTIAL RISKS FOLLOWING PROLONGED USE AFTER
20 WEEKS OF PREGNANCY**

The Medicines and Healthcare products Regulatory Agency (MHRA) want to remind healthcare professionals that use of systemic (oral and injectable) NSAIDs such as ibuprofen, naproxen, and diclofenac is contraindicated in the last trimester of pregnancy (after 28 weeks of pregnancy).

A review of data from a 2022 study has identified that prolonged use of NSAIDs from week 20 of pregnancy onwards may be associated with an increased risk of oligohydramnios (low levels of amniotic fluid surrounding the baby) and fetal renal dysfunction. Some cases of constriction of the ductus arteriosus (narrowing of a connecting blood vessel in the baby's heart) have also been identified at this early stage.

If, following consultation between the patient and a healthcare professional, use of a systemic NSAID after week 20 of pregnancy is considered necessary, it should be prescribed for the lowest dose for the shortest time and additional neonatal monitoring considered if used for longer than several days. This is in addition to giving advice to discontinue use of any NSAID in the last trimester of pregnancy.

Advice for healthcare professionals:

- The MHRA remind healthcare professionals that systemic (oral and injectable) NSAIDs are contraindicated during the last trimester (after 28 weeks) of pregnancy due to the risk of premature closure of the ductus arteriosus and renal dysfunction in the fetus and due to prolongation of maternal bleeding time and inhibition of uterine contractions during labour
- a review of data from [a 2022 study](#) has identified that prolonged use of NSAIDs from week 20 of pregnancy onwards may be associated with an increased risk of:
 - oligohydramnios resulting from fetal renal dysfunction; this may occur shortly after initiation, although it is usually reversible upon discontinuation.
 - cases of constriction of the ductus arteriosus, most of which resolved after treatment cessation
- avoid prescribing systemic NSAIDs from week 20 of pregnancy unless clinically required and prescribe the lowest dose for the shortest time in these circumstances
- antenatal monitoring for oligohydramnios should be considered if the mother has been exposed to NSAIDs for several days after week 20 of pregnancy; the NSAID should be discontinued if oligohydramnios is found or if the NSAID is no longer considered to be clinically necessary
- please advise patients who are pregnant to avoid use of NSAIDs available without prescription from week 20 of pregnancy onwards unless advised by their healthcare professional
- continue to follow clinical guidelines about taking and recording current and recent medicines, including over-the-counter medicines, at each antenatal appointment (for example, see [NICE guideline on antenatal care \[NG201\]](#))
- report suspected adverse reactions to NSAIDs to the [Yellow Card scheme](#)

Advice for healthcare professionals to provide to patients:

New information for patients about NSAIDs in pregnancy

- NSAID (non-steroidal anti-inflammatory) medicines such as ibuprofen, naproxen, and diclofenac are well established medicines for short-term pain relief, but all NSAIDs have recognised side effects and these are listed in the Patient Information Leaflet
- this advice is for oral NSAIDs (taken by mouth) and NSAIDs administered by injection
- if you are pregnant and are worried about taking a NSAID, please discuss this with a healthcare professional who will be able to advise further on your treatment plan
- NSAID should not be taken during the third (last) trimester of pregnancy (after 28 weeks of pregnancy) as they can in some cases cause labour to be delayed or last longer than expected. It can also have potential effects on the unborn baby's kidneys and heart
- while it is already well known that NSAIDs should not be taken during the third trimester of pregnancy, new information has identified that there may be potential risks to the baby following prolonged use of a NSAID after week 20 of pregnancy
- this new evidence has shown that prolonged use of NSAIDs after week 20 of pregnancy may increase the risk of problems with the unborn baby's kidneys and heart – however, these effects are usually reversible when the NSAID is stopped
- NSAIDs should be avoided from week 20 of pregnancy onwards unless absolutely necessary and advised by your healthcare professional
- if you and your doctor decide you should take a NSAID during pregnancy, then this should be at the lowest dose for the shortest period
- if you are treated with an NSAID during later pregnancy for more than a few days, your doctor may recommend additional monitoring such as ultrasound scans to check on your baby's health
- it is vitally important that you seek medical advice if pain persists for longer than 3 days or if you have repeated pain during pregnancy

General advice about pain relief during pregnancy

- some patients may need short-term pain relief during pregnancy, such as for headache, toothache, muscle or joint pain and will need to take a medicine to help relieve their pain
- if you are unsure whether your pain relief medicine is an anti-inflammatory (NSAID), please speak to your doctor, midwife, or pharmacist
- some non-prescription pain relief medicines may contain more than one active drug, therefore it is important to read the box or the leaflet provided with the medicine to see if it contains an NSAID like ibuprofen
- if you have concerns about pain or inflammation or are not certain which medicines to take while you are pregnant, talk to your midwife or a healthcare professional
- the use of any non-prescription medicine for the management of pain during pregnancy should be for the shortest possible time at the lowest possible dose
- if pain persists for longer than 3 days, or if you have repeated pain during pregnancy, then you should seek advice from your doctor or another healthcare professional

Background

NSAIDs block the synthesis and release of prostaglandin to relieve pain and inflammation. NSAIDs include ibuprofen, naproxen, and diclofenac, which are sold under many different brand names. The advice in this article applies to oral NSAIDs and NSAIDs administered by injection (available on prescription).

NSAIDs are contraindicated in the third trimester of pregnancy. This means they should not be used from week 28 of pregnancy. This is due to the increased risks of constriction of the ductus arteriosus and renal dysfunction, which are greater in the last trimester. NSAIDs may also increase bleeding time owing to their anti-platelet-aggregating effect on platelets and may inhibit uterine contractions, resulting in delayed or prolonged labour.

New review of safety data

A [recent European review](#) considered further evidence on the risks of NSAIDs in pregnancy. The review recommended that additional warnings should be added to the product information highlighting the risks of oligohydramnios (reduced volume of amniotic fluid surrounding baby) and constriction of the ductus arteriosus (a blood vessel in the baby's heart) if NSAIDs are used for more than a few days after week 20 of pregnancy. Oligohydramnios and constriction of the ductus arteriosus are

potentially serious as they can cause restriction of fetal growth and heart dysfunction.

Evidence was identified from an [observational cohort study](#)¹ of data between 2008 and 2017 reporting that oligohydramnios, likely caused by fetal renal dysfunction, was associated with use of NSAIDs from week 20 of pregnancy. From a total of 1092 pregnancies exposed to NSAIDs during the second and/or third trimester, 41 (3.8%) cases of oligohydramnios were observed. This compares to 29 (2.5%) from a total of 1154 pregnancies exposed to NSAIDs in the first trimester.

In the same study, a small number of reports of premature closure of the ductus arteriosus was observed in pregnancies following exposure to NSAIDs during the second or third trimester. There were no reports relating to exposure during the first trimester. The study also looked at the effects of metamizole exposure in pregnancy, a different pain relief medicine not available in the UK.

MHRA review and independent advice

The findings of this study were considered by the Paediatric Medicines and Medicines in Women's Health Expert Advisory Groups of the [Commission on Human Medicines](#) (CHM), and by the CHM, which agreed with the recommendations of the European review.

The CHM considered that the risk of constriction of the ductus arteriosus with prolonged exposure was serious and that this supported the updated warnings in the product information, although it noted there was limited evidence for the risk with short-term (less than a few days) exposure to NSAIDs during the late second trimester. If NSAID treatment is considered by a doctor to be necessary, then antenatal monitoring for oligohydramnios and constriction of the ductus arteriosus should be undertaken from week 20 onwards.

The product information for NSAIDs has been amended to include the risk of oligohydramnios and premature closure of the ductus arteriosus in the second trimester of pregnancy. It now includes advice to avoid use from week 20 of pregnancy onwards unless considered necessary by a doctor.

Advice about pain relief in pregnancy

It is recognised that some patients may need short-term pain relief during pregnancy, such as for headache, toothache, muscle or joint pain. Before using any pain relief medicine available without prescription during pregnancy, patients should be advised to read the Patient Information Leaflet and only use the medication for the shortest possible time at the lowest possible dose and lowest possible frequency.

If pain persists beyond 3 days, then patients should seek advice from their doctor or healthcare professional. Patients should be made aware that some pain relief medicines, available without prescription, may contain multiple active ingredients,

¹ Dathe K and others, [Fetal adverse effects following NSAID or metamizole exposure in the 2nd or 3rd trimester](#). BMC Pregnancy and Childbirth 2022; issue 22, article number 666

like ibuprofen and paracetamol, codeine and paracetamol, or codeine and ibuprofen. Therefore, they should check the Patient Information Leaflet supplied with the medicine for further information and speak to a healthcare professional if they have questions.

Medicines not included in this advice

The review did not examine topical NSAIDs (gels and creams containing NSAIDs). Healthcare professionals should follow the contraindications and warnings in the product information in relation to pregnancy. Patients who are using gel or creams containing NSAIDs during pregnancy should be advised to read the Patient Information Leaflet for advice.

The latest review did not include consideration of COX-2 inhibitor pain relief medicines (Coxib) medicines. However, it should be noted that all Coxibs are contraindicated in the third trimester of pregnancy, and some are contraindicated throughout all of pregnancy. Coxibs inhibit prostaglandin synthesis, similarly to other NSAIDs, and have been associated with oligohydramnios, uterine inertia and premature closure of the ductus arteriosus. Healthcare professionals should follow the contraindications and warnings in the product information for the COX-2 inhibitor drugs in relation to pregnancy.

Report suspected adverse drug reactions

Please continue to report any suspected adverse drug reactions via the Yellow Card Scheme. Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the [Yellow Card website](#)
- the Yellow Card app; download from the [Apple App Store](#) or [Google Play Store](#)
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

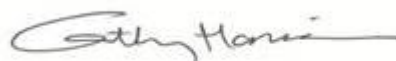
When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates. When reporting for a biological medicine or vaccine, please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch number.

The complete MHRA Drug Safety update is available at the following link [MHRA Drug Safety Update-Non-steroidal anti-inflammatory drugs \(NSAIDs\): potential risks following prolonged use after 20 weeks of pregnancy](#).

Yours sincerely



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Chief Medical Officer



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This letter is available on the Department of Health website at
<https://www.health-ni.gov.uk/topics/professional-medical-and-environmental-health-advice/hssmd-letters-and-urgent-communications>