Medicines Adverse Reactions Committee

Meeting date	**8 June 2017**	Agenda item	3.2.2	
Title	**NSAIDs and spontaneous abortion**			
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice	
Active constituents	**Dose forms**		**PHARMAC funding**	**OTC products**
Ibuprofen	Oral:	tablet, capsule, liquid	Y (tablet, liquid)	Y
Diclofenac	Oral:	tablet, capsule	Y (tablet)	Y
	Ophthalmic:	eye drops	Y	
	Injection:	solution	Y	
	Rectal:	suppository	Y	
Naproxen	Oral:	tablet	Y	Y
Mefenamic acid	Oral:	capsule	Y	Y
Meloxicam	Oral:	tablet	Y	
Tenoxicam	Oral:	tablet	Y	
Celecoxib	Oral:	capsule		
Etoricoxib	Oral:	tablet		
Parecoxib	Injection:	powder		
Ketoprofen	Oral:	capsule	Y	
Ketorolac	Ophthalmic:	eye drops		
Sulindac	Oral:	tablet	Y	
Flurbiprofen	Oromucosal:	lozenge		Y
Benzydamine	Oromucosal:	lozenge, mouth gel, mouthwash, throat spray	Y (mouthwash)	Y
Previous MARC meetings	NSAIDs in pregnancy and neonates (107th meeting on 5 September 2001) where 2 papers were reviewed neither relating to spontaneous abortion.			
International action	TGA safety review October 2016 (Annex 1) FDA review of pain medicine use during pregnancy January 2015			
Prescriber Update	None			
Schedule	Varies from general sale to prescription only			
Usage data	Those that are available OTC and/or PHARMAC funded likely to have higher use. Please refer to section 2.5 for further information.			
Advice sought	**The Committee is asked to advise whether:** – There is sufficient evidence for an association between NSAIDs included in this review and spontaneous abortion. – Updates to the data sheets are necessary. If yes, what information should this include? Should these updates be required for eye drop preparations? – Medsafe should consult on updates to the required warning and advisory statements for NSAID OTC products. – This requires further communication other than MARC's Remarks in *Prescriber Update.* – Any other regulatory action is required.			

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1.0 PURPOSE

On 11 October 2016, the Therapeutic Goods Administration (TGA) of Australia released their safety review on nonsteroidal anti-inflammatory drugs (NSAIDs) and spontaneous abortion. The TGA reviewed data sheets and package warnings for information on the potential increased risk of miscarriage due to exposure in early pregnancy.

The purpose of this paper is to review the information on the risk of spontaneous abortion with the use of NSAIDs. Aspirin and indometacin are excluded from this review due to the conditions they are used to prevent or treat. Topical preparations such as gels and skin sprays are also excluded from this review as systemic absorption from these formulations is expected to be low. Oromucosal products are included since these are swallowed and systemically absorbed.

2.0 BACKGROUND

2.1 NSAIDs

NSAIDs relevant to this review are listed on the cover page.

NSAIDs are used for the treatment of pain, inflammation and fever. Aspirin is also used for the treatment of acute coronary syndrome and to inhibit platelet aggregation. Low-dose aspirin may also be used in women who have an increased chance of developing pre-eclampsia. Indometacin is indicated for the closure of patent ductus arteriosus in premature babies. Due to the additional uses of aspirin and indication for indometacin, these medicines are excluded from this review.

NSAIDs are available in various dose forms and routes of administration. Some dose forms are easily accessible as general sales medicines or pharmacy only medicines. Systemic preparations include formulations intended for oral, rectal or parenteral administration. Ophthalmic products are also available in the form of eye drops. Excess drug from ophthalmic preparations can drain through the tear duct and be systematically absorbed via the nasal mucosa potentially leading to systemic adverse reactions and therefore are included in this review. Oromucosal products are included since these are swallowed and systemically absorbed. Topical preparations are excluded from this review as systemic absorption is expected to be low.

The primary effect of NSAIDs is to inhibit cyclooxygenase (COX; prostaglandin synthase) thereby impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin and thromboxanes (Figure 1) [1]. Two related isoforms of the COX enzyme have been well characterised: COX-1 and COX-2. A splice variant derived from the COX-1 gene has been described as COX-3. The relevance of this isoform is still unclear.

The degree of inhibition of an isoform of COX may affect an NSAID's activity and toxicity [1]. There are differences in the regulation and expression of these enzymes in various tissues [1]:

- COX-1 is expressed in most tissues but variably. It is described as a "housekeeping" enzyme, regulating normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function) and is stimulated by hormones or growth factors.
- COX-2 is usually undetectable in most tissues; its expression is increased during states of inflammation or experimentally in response to mitogenic stimuli. COX-2 is constitutively expressed in the brain, kidney, bone and probably in the female reproductive system. COX-2 has an important role in the inflammatory process although the effect of COX-2 inhibition on inflammation is not completely understood.

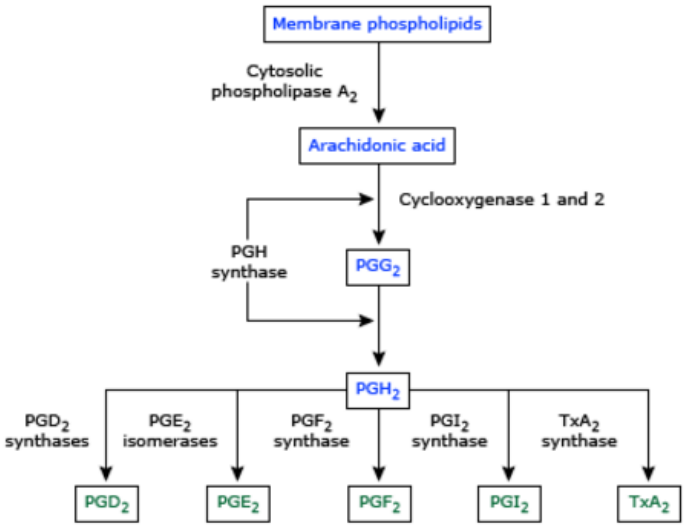

Figure 1: Prostaglandin and thromboxane synthesis

2.2 Spontaneous abortion

Spontaneous abortion (miscarriage) is a pregnancy that ends on its own within the first 20 weeks of gestation [2]. The World Health Organization defines it as expulsion or extraction of an embryo or fetus weighing 500 g or less [2].

Spontaneous abortion is the most common complication of early pregnancy [2]. Up to 50% of all miscarriages are thought to occur soon after implantation [3]. 99% of spontaneous abortions occur in the first 12 to 14 weeks of pregnancy (1st trimester) [3]. The incidence of spontaneous abortion in clinically recognised pregnancies up to 20 gestational weeks is 8-20% [2]. However, the incidence among women who have previously had a child is much lower (5%) [2]. The overall risk of spontaneous abortion after 15 weeks is low (about 0.6%) for chromosomally and structurally normal fetuses [2].

Loss of unrecognised or subclinical pregnancies is high, occurring in 13-26% of all pregnancies [2]. Early pregnancy losses are unlikely to be recognised unless daily pregnancy tests are performed [2].

Vaginal bleeding during pregnancy may be the first sign of a spontaneous abortion [3]. However, about 20% of women have vaginal bleeding during the first 12 weeks of pregnancy and less than half of them miscarry [3]. Other symptoms include abdominal and back pain and uterine cramping [4].

For women in their childbearing years, the chances of having a spontaneous abortion range from 10-25% [3]. Risk factors include [3]:

- Health: the risk is lower in healthy women, where the average risk is about 15-20%.
- Maternal age:
    - < 35 years: 15% chance
    - 35-45 years: 20-35% chance
    - > 45 years: up to 50% chance.
- Previous miscarriage: a woman who has had a previous miscarriage has a 25% chance of having another (only a slightly higher risk than for someone who has not had a previous miscarriage).

Use of some medicines and substances (eg, smoking, alcohol) is also a risk factor. The use of NSAIDs around the time of conception may be associated with an increased risk of miscarriage. The postulated mechanism is that prostaglandin inhibitors interfere with the role prostaglandins play in implantation, therefore potentially leading to abnormal implantation and pregnancy failure [2].

Spontaneous abortion is most commonly caused by chromosomal abnormalities in the embryo or exposure to teratogens [2]. It is often difficult to determine the cause of a spontaneous abortion in an individual case [2].

Comments:

It is thought that NSAIDs interfere with the role of prostaglandins during implantation resulting in a spontaneous abortion.

Symptoms of spontaneous abortion such as abdominal pain, back pain and uterine cramps could lead to a woman using an NSAID for relief without knowing she is pregnant.

2.3 Data sheets

2.3.1 New Zealand

A summary of information on use during pregnancy for NSAID-containing products in NZ data sheets is provided in Table 1. This information is correct as at 2 May 2017. As some NSAID-containing products are available as general sales or pharmacy only medicines, not all products have accompanying data sheets.

Table 1: Summary of information on use during pregnancy (2 May 2017)

Product name	Contraindicated in 3rd trimester?	Use in pregnancy
Ibuprofen		
Brufen & Brufen SR tablets	Y	Information as required for European data sheets (see section 2.3.3).
Fenpaed oral suspension	Y (pregnancy)	Avoid during pregnancy if possible. Congenital abnormalities have been reported in association with ibuprofen administration in man; however these are low in frequency and do not appear to follow any discernible pattern. Information on use during latter part of pregnancy (closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, delay labour and birth).
Ibugesic tablets	Y	Information on use during latter part of pregnancy (closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, delay labour and birth).
Ibuprofen (Actavis) tablets	Y	Information on use during latter part of pregnancy (closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, delay labour and birth).
Diclofenac		
Apo-Diclo EC, SR tablets	N	Should be avoided in pregnancy unless the benefits outweigh the potential risk to the fetus. Information on use during last 3 months of pregnancy (closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, delay labour and birth).
Diclax SR tablets	Y	Should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the fetus. Information on use during third trimester (uterine inertia and/or premature closure of the ductus arteriosus).
Diclofenac (Dr Reddy's) tablets	N	Employed only for compelling reasons and only in the lowest effective doses.

		Information on use during last 3 months of pregnancy (uterine inertia and/or premature closure of the ductus arteriosus).
Diclofenac Sandoz tablets	Y	Information for use during the different trimesters of pregnancy requires re-ordering as this information is currently confusing.
Voltaren EC tablets, injection, suppositories, D tablets, SR tablets (Novartis)	Y	Should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. Information on use during third trimester (uterine inertia, fetal renal impairment with subsequent oligohydramnios and/or premature closure of the ductus arteriosus).
Voltaren Ophtha eye drops (Novartis)	N	General information on systemic diclofenac in pregnant mice and rats. Animal studies have so far shown no risk to the fetus during the first and second trimesters of pregnancy, but no controlled studies in pregnant women are available. Voltaren Opththa should not be used during the third trimester of pregnancy (possible risk of premature closure of ductus arteriosus and possible inhibition of contractions).
Voltaren Osteo tablets (GSK)	Y	Information for use during the different trimesters of pregnancy requires re-ordering as this information is currently confusing.
Voltaren Rapid tablets (GSK)	Y	Should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. Information on use during third trimester (uterine inertia, premature closure of the ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, delay labour and birth).
Naproxen		
Naprosyn SR tablets	N	Information on use during latter part of pregnancy (closure of the fetal ductus arteriosus, prolong labour and delay birth). Should only be administered during pregnancy if the benefits justifies the potential risk.
Naxen tablets	N	Information on use during latter part of pregnancy (closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, delay labour and birth).
Noflam tablets	N	Information on use during latter part of pregnancy (closure of the fetal ductus arteriosus, prolong labour and delay birth). Should only be administered during pregnancy if the benefits justifies the potential risk.
Sonaflam tablets	N	As with other medicines of this type, naproxen produces delay in parturition in animals and also affects the human fetal cardiovascular system (closure of ductus arteriosus). Therefore, naproxen sodium should not be used during pregnancy unless clearly needed.

Mefenamic acid		
Ponstan capsules	N	Should only be used if the potential benefits to the mother justify the possible risks to the fetus. Information on use of NSAIDs during latter part of pregnancy (closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, delay labour and birth). Because of this, mefenamic acid in pregnant women is not recommended and should be avoided during the third trimester of pregnancy including the last few days before expected birth. Information on prolongation of pregnancy and interference with labour when administered late in pregnancy. Inhibition of prostaglandin synthesis by NSAIDs may adversely affect pregnancy. Epidemiological studies suggest an increased risk of spontaneous abortion after use in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss. If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases.
Meloxicam		
Arrow – Meloxicam tablets	Y (pregnancy or lactation)	Information as required for European data sheets (see section 2.3.3).
Meloxrex tablets	Y (pregnancy or lactation)	Information as required for European data sheets (see section 2.3.3).
Mobic tablets	Y (pregnancy or lactation)	Information as required for European data sheets (see section 2.3.3).
Tenoxicam		
Reutenox tablets	Y	Information as required for European data sheets (see section 2.3.3).
Tilcotil tablets	Y	Information as required for European data sheets (see section 2.3.3).
Celecoxib		
Celecoxib capsules (Pfizer)	N	Not recommended in pregnancy unless it is considered clinically essential. Use during the third trimester of pregnancy should be avoided and should not be used during first and second trimesters unless potential benefit to the mother justifies the potential risk to the fetus. If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Information on use of celecoxib in pregnant rats. Inhibition of prostaglandin synthesis by NSAIDs may adversely affect pregnancy. Epidemiological studies suggest an increased risk of spontaneous abortion after use in early pregnancy. In animals, administration of prostaglandin

		synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.
Celostea capsules	N	Not recommended in pregnancy unless it is considered clinically essential. Use during the third trimester of pregnancy should be avoided and should not be used during first and second trimesters unless potential benefit to the mother justifies the potential risk to the fetus. Information on use of celecoxib in pregnant rats. Inhibition of prostaglandin synthesis by NSAIDs may adversely affect pregnancy. Epidemiological studies suggest an increased risk of spontaneous abortion after use in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.
Etoricoxib		
Arcoxia tablets	N	As with other medicines known to inhibit prostaglandin synthesis, use of Arcoxia should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus. Information on reproductive studies conducted in rats. Should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus.
Parecoxib		
Dynastat injection	N	General information on parecoxib animal reproductive studies conducted in rats and rabbits. Parecoxib increased post-implantation losses in rats and rabbits at doses that resulted in systemic exposures (plasma AUC) to valdecoxib that were similar to the human exposure at the maximum recommended therapeutic dose. This effect is thought to be a consequence of the inhibition of prostaglandin synthesis and has been reported to occur with other NSAIDs. Use of COX inhibitors may result in premature closure of ductus arteriosus or uterine inertia. Therefore, use during the third trimester should be avoided. Inhibition of prostaglandin synthesis by NSAIDs may adversely affect pregnancy. Epidemiological studies suggest an increased risk of spontaneous abortion after use in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.
Ketoprofen		
Oruvail SR capsules	Y	Use during first and second trimester of pregnancy should be avoided. Information on use during the latter part of pregnancy (closure of fetal ductus arteriosus, renal toxicity). Information on use at term (prolonged labour and delayed parturition and prolonged bleeding time in both mother and child).

Ketorolac		
Acular eye drops	N	Not recommended in pregnancy. Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Sulindac		
Aclin tablets	N	Should not be given to pregnant women since safety for its use has not been established. Information on use during the third trimester of pregnancy (closure of the fetal ductus arteriosus, tricuspid incompetence and pulmonary hypertension, non-closure of ductus arteriosus, myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis, oligohydramnios, gastrointestinal bleeding or perforation, increased risk of necrotising enterocolitis, delayed labour and birth).

Comments:

NSAIDs relevant to this review that do not have any data sheets are Strepfen flurbiprofen lozenges and the Difflam benzydamine range of products.

Most data sheets have a general statement about considering the benefits and risks when used during pregnancy.

First and second trimesters: Information varies depending on the substance. Some data sheets specifically mention spontaneous abortion or miscarriage (Brufen, Ponstan, all meloxicam products, all tenoxicam products, all celecoxib products, parecoxib).

Third trimester: Generally, all data sheets contain information on use during the third trimester. However, not all data sheets have a contraindication against use during the third trimester.

NSAIDs with many different brands: Information in various product data sheets for ibuprofen, diclofenac and naproxen vary.

COX-2 inhibitors: There are currently three COX-2 inhibitors available in NZ: celecoxib, parecoxib, etoricoxib. The parecoxib and celecoxib data sheets mention pre- and post-implantation loss and spontaneous abortion; the etoricoxib data sheet does not mention pre- and post-implantation loss, spontaneous abortion or miscarriage.

2.3.2 Australia

TGA's review showed that the risk of spontaneous abortion is inconsistently included in Australian data sheets across the various non-aspirin NSAIDs. Five non-aspirin NSAIDs (ibuprofen, mefenamic acid, piroxicam, celecoxib and parecoxib) include a statement warning of increased risk of miscarriage.

Some of these data sheets include a statement regarding increased pre-implantation and post-implantation losses in animal studies with no link to the clinical effect of an increased risk of spontaneous abortion. Although many data sheets do not specifically document the risk of spontaneous abortion, they note that the product should not be used in pregnancy unless the benefits outweigh the risks.

The assessment concluded that the data sheets of all systemic and ophthalmic non-aspirin NSAIDs should be harmonised to include warnings regarding the increased risk of spontaneous abortion when NSAIDs are taken around the time of conception. The update requested by the TGA was as follows:

Use in pregnancy:

Epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

2.3.3 Europe

In 2004, the European Medicines Agency's (EMA) Pharmacovigilance Working Party (PhVWP) recognised an increased risk of miscarriage associated with prostaglandin synthesis inhibitors. The class labelling approved by PhVWP (www.ogyei.gov.hu/dynamic/PhVWP_ajanalsok//2004_pdf/NSAID_pregnancy2004.pdf) for the European data sheets for NSAIDs (including selective COX-2 inhibitors) is provided below:

4.3 Contraindication

Third trimester of pregnancy

4.6 Pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, [medicine name] should not be given unless clearly necessary. If [medicine name] is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- *cardiopulmonary toxicity (with premature closure of the ductus arteriosis and pulmonary hypertension);*
- *renal dysfunction, which may progress to renal failure with oligo-hydroaminiosis;*

the mother and the neonate, at the end of pregnancy, to:

- *possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.*
- *inhibition of uterine contractions resulting in delayed or prolonged labour*

Consequently, [medicine name] is contraindicated during the third trimester of pregnancy.

2.3.4 Canada

Canadian data sheets have a consumer information section (Part II). Information that should be included in the consumer information section of NSAID data sheets include:

Warnings and Precautions:

- *If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than [medicine name]:*

  Current pregnancy (less than 28 weeks)

- *Also, before taking this medication, tell your health care provider if you are planning to get pregnant.*
- *While taking this medication: fertility may be decreased. The use of [medicine name] is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping [medicine name] should be considered.*

2.4 Warning and advisory statements

2.4.1 New Zealand

The Label Statements Database (LSD) lists the warning and advisory statements that are required on medicine labels (eg, on OTC packs). The statements relevant to this safety concern are:

> *Do not use [product name] during the first 6 months of pregnancy, except on the advice of a healthcare professional.*
>
> *Do not use at all during the last 3 months of pregnancy.*

These warning statements are required for the following OTC products:

- diclofenac when available as an OTC medicine for oral use
- ibuprofen when available as general sale, pharmacy-only or pharmacist-only medicine in a solid oral dose form.

These warning statements are not required for the following OTC products:

- ibuprofen when pharmacy-only in liquid oral dose form; for external use
- mefenamic acid
- naproxen
- flurbiprofen.

Comments:

The required pregnancy-related warning and advisory statements in NZ are the same as those currently required by the TGA. The TGA has proposed some alternative wording to more appropriately address the risk of spontaneous abortion (refer to section 2.4.2). Many products have packaging that is aligned between NZ and Australia so it is possible that the change in the warning statement required by the TGA will result in similar changes for NZ.

The TGA were particularly concerned that pregnancy-related warning and advisory statements for products indicated for dysmenorrhoea are not required. This is of concern because pre-emptive treatment of dysmenorrhoea is recommended and an implantation bleed can mimic the start of menstruation. Therefore, women who have conceived but are not yet aware could take an NSAID for dysmenorrhoea. In NZ, this concern is applicable to Ponstan (mefenamic acid 250 mg capsule) and Naprogesic (naproxen 275 mg tablet) which have label claims for the relief of period pain.

It is worth noting that these warning statements are only required for ibuprofen when available in a solid oral dose form; oral liquid preparations are exempt.

2.4.2 Australia

The Required Advisory Statements for Medicine Labels (RASML) is the TGA's equivalent to Medsafe's label statements database (LSD).

The TGA has proposed some alternative wording to more appropriately address the risk of spontaneous abortion. Following public consultation (www.tga.gov.au/submissions-and-tga-response-non-steroidal-anti-inflammatory-drugs-proposed-additional-advisory-statement) the TGA is requiring the following warning statement:

> *Do not use if trying to become pregnant, or during the first 6 months of pregnancy except on doctor's advice. Do not use at all during the last 3 months of pregnancy.*

This warning statement will be required for all oral non-aspirin NSAIDs (diclofenac, flurbiprofen, ibuprofen, ketoprofen, mefenamic acid and naproxen) purchased OTC even if they are for children under 12 years of age or specifically indicated for period pain.

It is not known what the implementation timeframe is but the warning statement will be included in the RASML document when it is next updated.

2.5 Usage data

The number of community pharmacy initial dispensings of prescriptions per month for diclofenac, ibuprofen and naproxen from July 2012 to June 2014 is shown in Figure 2.

Figure 2: Number of community pharmacy initial dispensings of prescriptions per month for A: diclofenac, B: ibuprofen and C: naproxen

2.6 TGA review

The review (www.tga.gov.au/alert/safety-review-nonsteroidal-anti-inflammatory-drugs-nsaids-and-spontaneous-abortion) was prompted as information on the potential risk of miscarriage after NSAID exposure in early pregnancy differed between naproxen data sheets. This issue was also referred to the Advisory Committee on the Safety of Medicines (ACSOM; TGA's MARC equivalent) for advice.

The review initially included aspirin but this was later excluded so that only non-aspirin NSAIDs are subject to the TGA's recommendations. Indomethacin was also excluded due to its indication (closure of patent ductus arteriosus in premature babies).

The TGA are requiring updates to data sheets (see section 2.3.2) and warning and advisory statements for OTC products (see section 2.4.2).

2.7 FDA review

The FDA reviewed the possible risks of pain medicine use during pregnancy and released a safety communication in January 2015 (www.fda.gov/Drugs/DrugSafety/ucm429117.htm). Research studies published in the medical literature were reviewed.

Three types of pain medicines used during pregnancy were included in the review:

- Prescription NSAIDs and risk of miscarriage in the first half of pregnancy. Products include those containing ibuprofen, diclofenac, naproxen and celecoxib.
- Opioids and risk of birth defects of the brain, spine or spinal cord in babies born to women who took these products during the first trimester of pregnancy.
- Paracetamol in both OTC and prescription products and the risk of attention deficit hyperactivity disorder (ADHD) in children born to women who took this medicine at any time during pregnancy.

All studies reviewed had potential limitations in their designs. Sometimes the accumulated studies on a topic contained conflicting results that prevented the FDA from drawing reliable conclusions. As a result, the FDA's recommendations on how pain medicines are used during pregnancy remain the same at this time. Health professionals should continue to follow existing recommendations in data sheets regarding use of analgesics during pregnancy.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Nielsen et al, 2001 – Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: Population based observational study and case-control study [5]

The authors performed a population based cohort study and a case-control study based on data in the Danish registries. The objective was to estimate the risk of adverse birth outcomes in women who take NSAIDs during pregnancy.

A case-control study was designed to investigate any association between NSAIDs and first recorded miscarriage. Cases (n=4268) were defined as first recorded miscarriages in women who had taken a prescription NSAID in the 12 weeks before date of discharge from hospital after miscarriage. The control group (n=29,750) was primiparous women who had live births.

Odds ratios for the dispensing of prescriptions in the weeks before miscarriage ranged from 6.99 (95%CI 2.75–17.74) when prescriptions were taken up during the last week before the miscarriage to 2.69 (95%CI 1.81–4.00) when taken up between 7 to 9 weeks before (Table 2). The ratio decreases as the time from taking up the prescriptions to discharge from hospital increases.

The authors conclude that use of NSAIDs during pregnancy does not seem to increase the risk of adverse birth outcome but is associated with increased risk of miscarriage.

Table 2: Odds ratios for miscarriage compared with pregnancies ending in a birth in women who took prescription NSAIDs

Variable	Miscarriage (n=4268)	Live birth (n=29 750)	Adjusted odds ratio (95% CI)
Time from taking up prescriptions for NSAIDs to date of discharge after miscarriage:			
1-12 weeks	63	318	1
1 week	3	9	6.99 (2.75 to 17.74)
2-3 weeks	5	15	3.00 (1.21 to 7.44)
4-6 weeks	14	41	4.38 (2.66 to 7.20)
7-9 weeks	19	92	2.69 (1.81 to 4.00)
10-12 weeks	22	161	1.26 (0.85 to 1.87)
Maternal age:			
<25 years (reference)	1022	8 284	1
25-29 years	1509	12 424	0.99 (0.91 to 1.07)
30-34 years	1128	6 728	1.36 (1.24 to 1.49)
>35 years	609	2 314	2.13 (1.91 to 2.38)
NSAIDs not prescribed during pregnancy	4205	29 432	

NSAIDs=non-steroidal anti-inflammatory drugs.
*Only primigravidas are included in the analysis.
The comparison period used for the reference group was the first trimester.

Comments:

Miscarriages were identified from the national Danish hospital discharge registry. This means that miscarriages that are clinically unapparent or those that do not require hospital admission are not included.

Prescriptions for NSAIDs were identified from a prescription database. There is no information on whether patients actually took these NSAIDs (actual use). There was no information on important confounders such as smoking and indication of NSAID use. There was also no data on OTC use of NSAIDs.

There was no information on gestational age at the time of miscarriage so a 12 week exposure period was chosen from the date of discharge. If the gestational age was <12 weeks, this period may overestimate exposure in the cases group which results in an overestimation of the association.

3.1.2 Li et al, 2003 – Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: Population based cohort study [6]

This population based prospective cohort study was designed to evaluate whether prenatal use of NSAIDs is associated with a risk of miscarriage. This effect was examined by analysing existing data from the authors' recently completed population-based cohort study of risk factors for miscarriage.

Data from the Kaiser Permanente Medical Care Program was used and prenatal use of NSAIDs, paracetamol and aspirin was ascertained by in-person interview. Paracetamol was used to control for potential confounding by indication. Pregnancy outcomes were measured up to 20 weeks of gestation.

Of the 2729 eligible women, 1063 (39%) participated and completed an interview conducted soon after each woman's pregnancy was confirmed. The final analysis included 1055 pregnant women. 53 women (5%) reported prenatal NSAID use around conception or during pregnancy. NSAID users were defined as those who reported using ibuprofen or naproxen after their last menstruation. Of the 162 women who experienced a miscarriage, 8% (13/162) had used non-aspirin NSAIDs during pregnancy compared to 4.6% (40/871) who did not miscarry. For aspirin, the proportion of women who miscarried and took aspirin (3%; 5/154) was closer to the proportion of women who did not miscarry and took aspirin (2%; 17/848).

Results are shown in Table 3. After adjustment for potential confounders (previous miscarriage, education, maternal age, gravidity, race, use of a Jacuzzi, multivitamin use, smoking since last menstruation), prenatal NSAID use was associated with an increased risk of miscarriage (adjusted HR 1.8; 95%CI 1.0–3.2). The association was stronger if the initial NSAID use was around the time of conception (adjusted HR 5.6; 95%CI 2.3–13.7) or if NSAID use lasted more than a week (adjusted HR 8.1; 95%CI 2.8–23.4).

Table 3: Prenatal use of NSAIDs by pregnant women and risk of miscarriage

	Miscarriage		
NSAID use	**Yes (n=162)**	**No (n=871)**	**Hazard ratio (95% CI)***
Non-users (n=980)†	149 (15)	831 (85)	1.0
Users (n=53):	13 (25)	40 (75)	1.8 (1.0 to 3.2)
Gestational age at first use:			
At conception (n=12)‡	6 (50)	6 (50)	5.6 (2.3 to 13.7)
After conception (n=40)	7 (18)	33 (83)	1.2 (0.5 to 2.6)
Duration of use:			
≤1 week (n=47)	9 (19)	38 (81)	1.3 (0.7 to 2.6)
>1 week (n=6)	4 (67)	2 (33)	8.1 (2.8 to 23.4)

*Adjusted for previous miscarriage, education, maternal age, gravidity, race, use of Jacuzzi or hot tub, multivitamin use, and smoked since last menstruation. Further adjustment for other variables listed in table 1 did not change the results.
†Used neither NSAIDs nor aspirin.
‡At conception: within the first week of gestational age.

There was weak evidence for an association between aspirin use and miscarriage (HR 1.6; 95%CI 0.6–4.1). The association was stronger when aspirin was first taken at the time of conception (HR 4.3; 95%CI 1.3–14.2), however this sample size was small (n=6). Prenatal use of paracetamol was not associated with increased risk of miscarriage regardless of timing and duration of use.

The authors conclude that prenatal use of NSAIDs and aspirin increased the risk of miscarriage. These findings need confirmation in studies designed specifically to examine the apparent association.

Comments:

In contrast to the study conducted by Nielsen et al, this Li et al study had more complete information on use of NSAIDs as it was based on actual use and included OTC use of NSAIDs. Ascertainment of miscarriage was also more complete.

However, this study has limitations because examining the association of NSAID use with miscarriage was not the primary aim of the original study. NSAID users were defined as those who used ibuprofen or naproxen and did not include all non-aspirin NSAIDs which could have underestimated exposure. The risk of miscarriage was mainly associated with NSAID use around conception which was not completely ascertained for all participants. The response rate was low.

3.1.3 Nielsen et al, 2004 – Danish group reanalyses miscarriage in NSAID users [7]

This letter to the editor was published in response to the study by Li et al. The authors accessed a recent update of their dataset covering 1998–2002, including gestational age, which was not originally accessible.

1599 women with first recorded miscarriage were identified. Of these, 45 had filled prescriptions for NSAIDs in the last 12 weeks before miscarriage. Controls were 10 primigravidas delivering after the 28th gestational week in the corresponding gestational period (n=15,990). Exposure was defined as those that redeemed NSAID prescriptions at appropriate gestational periods.

The association between miscarriage and NSAID use in five periods before miscarriage was consistently positive in the weeks before miscarriage with odds ratios from 3.35 to 0.58 (Table 4). There was a trend towards a stronger association when looking at periods closer to miscarriage.

Table 4: Association between miscarriage and NSAID use

	Without gestational age[2]		Including gestational age (new analysis)			
Week before miscarriage	Odds ratio	95% CI	Cases exposed to NSAIDs (n=1554)	Controls exposed to NSAIDs (n=15 677)	Odds ratio	95% CI
1	6.99	2.75-17.74	3	8	3.35	0.88 to 12.79
2-3	3.00	1.21-7.44	5	33	1.50	0.58 to 3.86
4-6	4.38	2.66-7.20	18	122	1.50	0.91 to 2.47
7-9	2.69	1.81-4.00	16	100	1.59	0.93 to 2.70
10-12	1.26	0.85-1.87	3	50	0.58	0.18 to 1.85

NSAIDs=non-steroidal anti-inflammatory drugs.

Comments:

This re-analysis of data gathered in the authors' 2001 study found a substantially reduced risk on their previously reported association between a prescription for NSAIDs and risk of miscarriage. All 95% confidence intervals overlap 1 indicating no association. Some of these intervals are also wide which indicates that the sample size was not large enough to detect a true association. The results should be interpreted with caution.

3.1.4 Nakhai-Pour et al, 2011 – Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion [8]

This nested case-control study used data from the Quebec Pregnancy Registry (QPR). The aim was to quantify the association between spontaneous abortion and types and dosages of non-aspirin NSAIDs in a cohort of pregnant women.

Women who had a spontaneous abortion were identified from the QPR, which is linked to three administration databases, including the RAMQ database (contains information on medical services, filled prescriptions, diagnoses, hospital admissions) and the Med-Echo database (records data on admissions to acute care hospitals for all residents of Quebec). For inclusion, women were required to be insured by the RAMQ drug plan which accounts for 36% of pregnant women in the region.

For each case, 10 controls were randomly selected from the remaining women in the registry and matched by index date (date of spontaneous abortion) and gestational age. Exposure to non-aspirin NSAIDs was defined as either having filled at least one prescription between the start of pregnancy and the index date, or as having filled a prescription before pregnancy the duration of which overlapped with the start of pregnancy.

Various confounding factors were accounted for in the analysis including sociodemographic characteristics, comorbidities in the year prior to pregnancy, use of medicines suspected of increasing the risk of spontaneous abortion, use of NSAIDs before pregnancy, use of health services in the year before pregnancy and history of planned or spontaneous abortion.

4705 cases (352 exposed) of spontaneous abortion and 47,050 controls (1213 exposed) were identified. Of the women with a spontaneous abortion, 7.5% (352/4705) had filled at least one prescription for non-aspirin

NSAIDs during pregnancy compared to 2.6% (1213/47,050) of women who did not have a spontaneous abortion. After adjustment for potential confounders, use of non-aspirin NSAIDs during pregnancy was significantly associated with the risk of spontaneous abortion (OR 2.43; 95%CI 2.12–2.79) (Table 5). The increased risk was consistent across all types of non-aspirin NSAIDs with the highest risk seen with diclofenac use (Table 6). No dose-response effect was observed.

Table 5: Crude and adjusted odds ratios for the association between use of non-aspirin NSAIDs during pregnancy and having a spontaneous abortion

Variable	OR (95% CI)	
	Crude	Adjusted*
No use of nonaspirin NSAIDs	1.00	1.00
Use of nonaspirin NSAIDs	3.06 (2.71–3.46)	2.43 (2.12–2.79)
Patient characteristics		
Age, yr	1.04 (1.03–1.04)	1.04 (1.03–1.04)
Urban residence	1.07 (1.00–1.15)	1.00 (0.92–1.08)
Receiving social assistance	1.23 (1.16–1.31)	1.06 (0.99–0.13)
Comorbidities during year before pregnancy		
None	1.00	1.00
Diabetes mellitus	1.69 (1.32–2.15)	1.25 (0.96–1.63)
Cardiovascular disease	1.22 (0.97–1.54)	0.83 (0.64–1.07)
Asthma	1.19 (1.10–1.28)	1.03 (0.94–0.13)
Untreated thyroid disease	1.40 (0.90–2.16)	1.15 (0.72–1.84)
Depression and/or anxiety	1.55 (1.37–1.75)	1.25 (1.08–1.45)
Systemic lupus erythematosus	2.00 (0.23–17.12)	0.54 (0.06–5.01)
Rheumatoid arthritis	1.41 (0.70–2.83)	1.12 (0.52–2.41)
Vsits to physicians during year before pregnancy, no.		
0–2	1.00	1.00
3–5	1.12 (1.03–1.22)	1.12 (1.03–1.23)
≥ 6	1.34 (1.25–1.44)	1.31 (1.20–1.44)
Different prescribers, no.		
0–2	1.00	1.00
≥ 3	1.21 (1.14–1.30)	0.93 (0.85–1.02)
Visited an emergency department or admitted to hospital during year before pregnancy		
No	1.00	1.00
Yes	1.08 (0.99–1.17)	0.88 (0.80–0.97)

Table 6: Association between use of non-aspirin NSAIDs and risk of spontaneous abortion

Variable	Controls *n = 47 050*	Cases *n = 4 705*	OR (95% CI)	
			Crude	Adjusted*
Type of NSAID				
None	45 837 (97.4)	4 353 (92.5)	1.00	1.00
Naproxen	435 (0.9)	133 (2.8)	3.22 (2.65–3.92)	2.64 (2.13–3.28)
Ibuprofen	258 (0.6)	61 (1.3)	2.49 (1.88–3.30)	2.19 (1.61–2.96)
Rofecoxib	152 (0.3)	39 (0.8)	2.70 (1.90–3.85)	1.83 (1.24–2.70)
Diclofenac	82 (0.2)	31 (0.7)	3.99 (2.63–6.03)	3.09 (1.96–4.87)
Celocoxib	111 (0.2)	30 (0.6)	2.85 (1.90–4.27)	2.21 (1.42–3.45)
Other	57 (0.1)	32 (0.7)	2.86 (1.93–4.23)	2.65 (1.71–4.12)
Combination	118 (0.2)	26 (0.6)	4.80 (3.02–7.65)	2.64 (1.59–4.39)
Maximum daily dose, %				
None	45 837 (97.4)	4 353 (93.0)	1.00	1.00
1–50	228 (0.5)	59 (1.3)	2.73 (2.05–3.64)	2.61 (1.90–3.59)
51–65	259 (0.6)	56 (1.2)	2.28 (1.70–3.05)	1.90 (1.39–2.61)
66–80	365 (0.8)	120 (2.6)	3.47 (2.81–4.27)	2.55 (2.03–3.21)
≥ 81	304 (0.6)	91 (1.9)	3.16 (2.49–4.00)	2.55 (1.96–3.32)
Unknown	57 (0.1)	26 (0.6)		

Note: CI = confidence interval, NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio.
*Odds ratios were adjusted for confounders listed in Methods.

Comments:

As with the study by Nielsen et al, this study had limitations around the lack of data on OTC use of NSAIDs and lack of information on indications for use. Usage of NSAIDs was ascertained from a database so it is not known if these were actually taken as prescribed. Spontaneous abortions that were not clinically detected were excluded.

Strengths include a large sample size, use of prospectively recorded information from databases rather than relying on patient recall and information on gestational age.

3.1.5 Daniel et al, 2014 – Fetal exposure to nonsteroidal anti-inflammatory drugs and spontaneous abortions [9]

This retrospective cohort study was based in a medical centre in Israel. The aim was to assess the risk of spontaneous abortion following maternal-fetal exposure to NSAIDs. Data was collected from a medicine dispensing database linked with two databases containing information on births and spontaneous abortions.

Time-varying Cox regression models were constructed and adjusted for maternal age, diabetes mellitus, hypothyroidism, obesity, hypercoagulation or inflammatory conditions, recurrent miscarriage, in vitro fertilisation of the current pregnancy, intrauterine contraceptive devices, ethnic background, tobacco use and year of admission. There were 2 main NSAID exposure groups: non-selective COX inhibitors (ibuprofen, diclofenac, naproxen, etodolac, indomethacin, lornoxicam, nabumetone) and COX-2 selective inhibitors (celecoxib, etoricoxib, rofecoxib). A woman was categorised as exposed if an NSAID had been dispensed between the first day of the last menstrual period and the day before the date of admission to hospital for a pregnancy that resulted in a spontaneous abortion or 20 weeks' gestation for pregnancies that ended with birth.

The cohort included 65,547 women who conceived during the study period. Of these, 58,949 (88.5%) were admitted for a birth and 7598 (11.4%) for spontaneous abortion. Of the women with spontaneous abortion, data about gestational age at admission were missing for 1090 (14.3%) women and were not included in the analysis. In total, 4495 of the 65,547 (6.9%) included pregnant women were exposed to NSAIDs during the study period, of which 4424 (98.4%) were exposed to non-selective COX inhibitors and 71 (1.6%) to selective COX-2 inhibitors.

Results are summarised in Table 7. There was a statistically significant association with exposure to non-selective COX inhibitors (crude HR 1.13; 95%CI 1.01–1.25). However, when the data was adjusted this association became non-significant (adjusted HR 1.10; 95%CI 0.99–1.22). A similar pattern occurred for selective COX-2 inhibitors however the point estimate and upper limit of the 95%CI was higher (crude HR 1.97, 95%CI 1.12–3.47; adjusted HR 1.43, 95%CI 0.79–2.59). The exposure group was also much smaller (n=71). There was no dose-response effect.

The authors conclude that no increased risk of spontaneous abortion following exposure to NSAIDs was found.

Table 7: Risk of spontaneous abortion following exposure to NSAIDs

				Spontaneous abortion hazard ratio (95% CI)	
Exposure	No. of participants	No. of abortions	Median gestational age at exposure, d	Unadjusted	Adjusted*
Not exposed	60 962	6 132			
Nonselective COX inhibitors	4 424	373	31	1.13 (1.01–1.25)	1.10 (0.99–1.22)
Ibuprofen	2 732	215	40	1.13 (0.98–1.30)	1.06 (0.93–1.22)
Diclofenac	919	93	23	1.21 (0.98–1.48)	1.19 (0.97–1.46)
Naproxen	671	53	27	1.87 (0.66–1.17)	0.97 (0.74–1.28)
Etodolac	272	4	20.5	1.26 (0.88 –1.80)	1.28 (0.91–1.79)
Indomethacin	132	15	89	3.54 (2.20–5.71)	2.82 (1.70–4.69)
COX-2 selective inhibitors	71	11	25	1.97 (1.12–3.47)	1.43 (0.79–2.59)

Note: CI = confidence interval, COX = cyclooxygenase.
*Adjusted for maternal age, hypothyroidism, diabetes mellitus, obesity, hypercoagulation state, uterine disorders, presence of an intrauterine contraceptive device, history of recurrent abortion, in vitro fertilization used to conceive the current pregnancy, inflammatory diseases and ethnic group (Bedouin v. Jewish).

Comments:

This study used data from dispensing database rather than a prescription database. The authors state that using dispensing data is a more accurate representation of actual use than using prescription data. This study did not account for OTC use of NSAIDs. However, it appears that only ibuprofen is available OTC in Israel. Data regarding gestational age and admission were missing for 14.3% of women whose pregnancy ended in spontaneous abortion. Again, this study could have missed spontaneous abortions that did not have a clinical presentation.

This study had a large sample size and used information from databases rather than relying on patient recall.

3.1.6 Velez Edwards et al, 2012 – Periconceptional over-the-counter nonsteroidal anti-inflammatory drug exposure and risk for spontaneous abortion [10]

The objective of this study was to estimate the association between over-the-counter NSAID exposure during the early first-trimester and risk of spontaneous abortion (gestation prior to 20 weeks) in a prospective cohort.

Women were enrolled in the Right from the Start study (2004–2010), which is a non-clinical, community-based pregnancy cohort. Exposure data regarding over-the-counter NSAID use from the last menstrual period through the 6th week of pregnancy were obtained from an intake interview and at enrolment and a computer assisted telephone interview at the end of the first trimester. Pregnancy outcomes were self-reported and verified by medical records. Gestational age was determined from last menstrual period. Stage of development prior to loss was determined from study ultrasound.

Cox proportional hazards regression models were used to estimate the association between NSAID exposure and pregnancy outcome, taking into account candidate confounders (maternal age, race/ethnicity, income, diabetes status, parity, gravidity, induced abortion history, study site, smoking status). Candidate confounders were analysed for independent association with both NSAID exposure and spontaneous abortion outcome. Those that were independently associated with NSAID exposure and spontaneous abortion outcome and that result in a 5% relative change in NSAID effect size estimates were retained in the model. No candidate met inclusion criteria. However, analyses adjusted for maternal age are also presented because this covariate was commonly included in multivariable models in previous studies.

Among 2780 pregnancies, 367 women (13%) experienced a spontaneous abortion. NSAID exposure was reported by 1185 (43%) women. Results are summarised in Table 8. NSAID exposure was not associated with spontaneous abortion risk in unadjusted models (HR 1.01, 95%CI 0.82–1.24) or models adjusted for maternal age (adjusted HR 1.00, 95% CI 0.81–1.23). A summary of the probability of loss by gestational age and NSAID exposure is shown in Figure 3.

The authors conclude that these findings suggest use of non-prescription over-the-counter NSAIDs in early pregnancy does not put women at increased risk of spontaneous abortion.

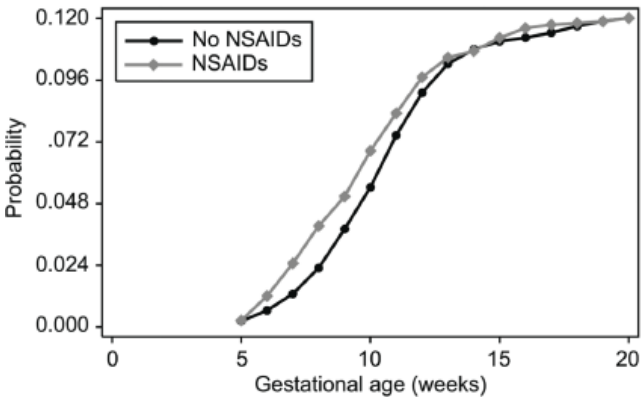

Figure 3: Cumulative probability of spontaneous abortion when exposed to NSAIDs

This figure shows the probability of miscarriage by NSAID exposure. Gestational age in weeks is provided on the x-axis and the y-axis indicates the cumulative probability of a spontaneous abortion.

Table 8: Cox regression analysis of first-trimester NSAID exposure analyses for spontaneous abortion

First-Trimester NSAID Exposure	Unadjusted HR	95% CI	Adjusted (aHR)	95% CI
None	1.00		1.00	
Any NSAID use	1.01	0.82, 1.24	1.00	0.81, 1.23
Any NSAID use (losses before 10 weeks)	0.95	0.72, 1.25	0.95	0.72, 1.25
Any NSAID use (losses 10 weeks or after)	1.09	0.80, 1.48	1.09	0.80, 1.48
Salicylates NSAID users (aspirin)	1.33	0.97, 1.81	1.31	0.96, 1.79
Excluding salicylates NSAID users (non-aspirin)	0.91	0.72, 1.15	0.91	0.72, 1.14
Total days of NSAID use†	1.01	0.99, 1.04	1.01	0.99, 1.04
0	1.00		1.00	
1–2	0.93	0.72, 1.21	0.91	0.70, 1.17
3–5	1.05	0.75, 1.46	1.05	0.75, 1.46
6–7	1.31	0.63, 2.69	1.32	0.65, 2.69
More than 7	1.05	0.62, 1.80	1.11	0.66, 1.89
Total days of NSAID use† (losses before 10 weeks)	1.02	0.99, 1.05	1.02	0.99, 1.05
0	1.00		1.00	
1–2	0.87	0.61, 1.23	0.84	0.59, 1.19
3–5	0.97	0.61, 1.53	0.98	0.62, 1.55
6–7	1.65	0.73, 3.73	1.64	0.74, 3.67
More than 7	1.11	0.55, 2.27	1.19	0.59, 2.39
Total days of NSAID use† (losses 10 weeks or after)	0.99	0.96, 1.03	0.99	0.96, 1.03
0	1.00		1.00	
1–2	1.01	0.69, 1.49	0.99	0.67, 1.46
3–5	1.14	0.70, 1.86	1.15	0.71, 1.87
6–7	0.76	0.19, 3.05	0.76	0.20, 3.03
More than 7	0.99	0.44, 2.24	1.05	0.47, 2.37

HR, hazard ratio; CI, confidence interval; aHR, adjusted HR for maternal age; NSAID, nonsteroidal anti-inflammatory drugs.

†Continuous refers to using days as a continuous outcome.

Comments:

This study excluded prescription use of NSAIDs. The authors note that the patients taking prescription NSAIDs are more likely to be taking higher doses and for other indications (eg, a chronic medical condition) which could reflect a different risk.

3.2 Company reports

Sections below summarise information provided by sponsors of NSAID-containing products. Medsafe requested information from innovator companies only. Specific information on systemic absorption from the use of eye drop preparations were requested from the relevant sponsors.

NSAIDs with highest use are likely to be ibuprofen and diclofenac based on OTC availability and PHARMAC funding. Information provided for ibuprofen products lacked detail and no response was received from sponsors of diclofenac (Voltaren) products.

3.2.1 Reckitt Benckiser

Reckitt Benckiser (RB) is the sponsor of Nurofen (ibuprofen) products.

Information provided by RB included:

- Australian Self-Medication Industry (ASMI) media statement on the TGA's review
- An industry position statement
- The TGA's web statement.

Comments:

These statements were related to the TGA's review and not specific to Nurofen. No data was presented by RB that could be evaluated. Nurofen is an OTC product and therefore does not have a data sheet. The current warning and advisory statements relating to pregnancy as required by the LSD do not apply to liquid dose forms of ibuprofen-containing products (eg, Nurofen for Children oral suspension).

3.2.2 Mylan/BGP Products

Mylan/BGP Products is the sponsor of Brufen (ibuprofen) tablets.

Mylan/BGP Products confirmed that the TGA safety advice did not contain any technical errors and did not have any further comments to add. The potential risk of NSAIDs and spontaneous abortion is noted in the data sheet and CMI (same information as that required in European data sheets).

3.2.3 Bayer

Bayer is the sponsor of Naprogesic (naproxen) tablets.

[redacted]

Comments:

Naprogesic is an OTC product and therefore does not have a data sheet. However, there are other naproxen-containing products that have data sheets. The current warning and advisory statements relating to pregnancy as required by the LSD do not apply to products containing naproxen.

3.2.4 Pfizer

Pfizer is the sponsor of Ponstan (mefenamic acid capsules), celecoxib capsules and Dynastat (parecoxib powder for injection).

Data sheets

Pfizer believes that the pregnancy precautions already articulated in the data sheets are consistent with currently available safety data. Pfizer will work collaboratively with Medsafe to ensure consistency in the information available to healthcare professionals.

3.2.5 Boehringer Ingelheim

Boehringer Ingelheim (BI) is the sponsor of Mobic (meloxicam) tablets.

[redacted]

[redacted]

Data sheet

Both the Mobic Company Core Data Sheet and the NZ data sheet note that data from epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor in early pregnancy, that Mobic is contraindicated in pregnancy and the use of Mobic may impair fertility and is not recommended in women attempting to conceive.

3.2.6 Roche

Roche is the sponsor of Tilcotil (tenoxicam) tablets.

[redacted]

[redacted]

Data sheets

The Tilcotil data sheet already includes information on the risk of miscarriage/abortion (same information as that required in European data sheets).

3.2.7 Merck Sharp & Dohme

Merck is the sponsor of Arcoxia (etoricoxib) tablets.

Background information

Etoricoxib is contraindicated in pregnancy and if a woman becomes pregnant during treatment, etoricoxib must be discontinued. As with other COX-2 inhibitors, the use of etoricoxib is not recommended in women attempting to conceive.

[redacted]

- [redacted]

3.2.8 sanofi-aventis

sanofi-aventis is the sponsor of Oruvail (ketoprofen) capsules.

[redacted]

Data sheets

Sanofi proposed not to update the Australian data sheet as requested by the TGA. Sanofi considered that the use in pregnancy subsection of the precautions section should remain unchanged.

Comments:
Although the Oruvail data sheet contains information on use during pregnancy, there is no mention on the suggestion of an increased risk of miscarriage.

3.2.9 Allergan

Allergan is the sponsor of Acular (ketorolac) eye drops.

[redacted]

Systemic absorption

The pharmacokinetics section of the NZ data sheet states:

> *Two drops (0.1 mL) of 0.5% Acular eye drops instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients' eyes (mean ketorolac concentrations 95 nanograms/mL aqueous humour, range 40-170 nanograms/mL). One drop (0.05 mL of 0.5% ketorolac trometamol solution was instilled into one eye and one drop of the vehicle into the other eye three times a day for 21 days in 26 normal subjects. Only 5 of 26 subjects had detectable amounts of ketorolac in their plasma (range 10.7 to 22.5 nanograms/mL) at Day 10 during topical ocular treatment. When ketorolac is given systemically to relieve pain, plasma levels following chronic systemic use average around 860 nanograms/mL.*

The above information indicates that the systemic absorption from topical ophthalmic dosing is very low compared to oral administration of ketorolac.

In summary, in 21 of 26 subjects exposed to ketorolac 0.5% topical ophthalmic solution, systemic levels were below the detectable limit in plasma. In the remaining 5 subjects, the plasma level was minimal compared to plasma levels following oral administration of ketorolac.

3.3 Case reports

3.3.1 New Zealand (CARM)

The Centre for Adverse Reactions Monitoring (CARM) has not received any cases of spontaneous abortions, missed abortions or stillbirths associated with NSAIDs.

3.3.2 Australia

Australian adverse event data was minimal for this association and provides limited support for a causal association. As at 21 January 2016, the TGA had received 3 reports for non-aspirin NSAIDs and spontaneous abortion (Table 9). Important information is missing from these cases including medical history, reproductive history and indication for use which may be confounding factors.

Table 9: ADR case details for non-aspirin NSAIDs and spontaneous abortion

Case number	Report entry date	Age (years)	Gender	Medicines reported as being taken	MedDRA reaction terms
189372	11/08/2003	31	Female	Nurofen (Ibuprofen) - Suspected Lyclear (Permethrin) - Suspected	Abortion spontaneous
217903	02/05/2006	-	Female	Advil (Ibuprofen) – Suspected	Abortion spontaneous
281764	20/04/2011	-	Female	Proxen SR (Naproxen) - Suspected	Abortion spontaneous

The TGA considers there is insufficient evidence to support a causal association between aspirin use and increased risk of miscarriage. As of 21 January 2016, the TGA had received 2 reports of aspirin and spontaneous abortion (Table 10). Information on medical history, reproductive history, concomitant medicines and indication for use is not included in these reports. Since aspirin may be used to prevent miscarriage in women with anti-phospholipid syndrome or recurrent miscarriages, the association reported in these cases may be confounded by underlying conditions predisposing these women to miscarriage.

Table 10: ADR case details for aspirin and spontaneous abortion

Case number	Report entry date	Age (years)	Gender	Medicines reported as being taken	MedDRA reaction terms
227671	18/04/2007	-	Female	Not specified (Aspirin) - Suspected Folic acid – not suspected	Abortion spontaneous
234558	18/10/2007	-	Female	Not specified (Aspirin) - Suspected	Abortion spontaneous

4.0 DISCUSSION AND CONCLUSIONS

NSAIDs inhibit prostaglandin synthetase. It is thought that prostaglandin inhibitors interfere with embryo implantation leading to abnormal implantation and pregnancy failure. There are NSAIDs that can be purchased over the counter as pharmacy-only medicines and ibuprofen can be purchased from a supermarket as a general sales medicine. Therefore, these products are potentially easily accessible with limited verbal advice or counselling from a healthcare professional.

Spontaneous abortion is a serious risk that can be distressing for a woman and their partner. 99% of spontaneous abortions occur in the first trimester. Loss of unrecognised or subclinical pregnancies is high, occurring in 13-26% of all pregnancies. Some symptoms of spontaneous abortion such as abdominal and back pain and uterine cramping could result in a woman taking an NSAID for symptom relief without knowing she is pregnant.

Studies investigating the association between use of NSAIDs in pregnancy and spontaneous abortion to date are all observational and results vary. Limitations of these studies include incomplete data on NSAID use and miscarriage. The reason for NSAID use is important because women in these studies could have used NSAIDs for symptoms of miscarriage (eg, cramping) so it is not possible to determine if NSAID use occurred before or after the onset of a miscarriage. Despite these limitations, the data suggests there could be an association between NSAID use and spontaneous abortion especially when an NSAID is taken close to the time of conception. There is also a suggestion that this could be a class effect as an increased risk is consistently seen with NSAIDs such as ibuprofen, diclofenac, naproxen, celecoxib and etoricoxib.

Due to ethical considerations around this safety concern, the strength of the evidence is unlikely to change significantly in the near future.

There seems to be agreement with the risks associated with taking NSAIDs in the third trimester of pregnancy. These risks include premature closure of the fetal ductus arteriosus and fetal impairment. At the end of pregnancy, NSAIDs may expose the mother and neonate to possible prolongation of bleeding time and inhibit uterine contractions which may result in delayed or prolonged labour. This is generally reflected in the NSAID data sheets although not all data sheets include a contraindication against use in the third trimester.

Information on the possible increased risk of spontaneous abortion is not included in all NSAID data sheets. In addition, warning statements are not required for all NSAIDs available OTC. The TGA are amending their warning statement to include women who are trying to become pregnant.

Data sheets could be updated to include information on spontaneous abortion such as:

> *Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss. During the first and second trimester of pregnancy, [medicine name] should not be given unless clearly necessary. If [medicine name] is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.*

The required warning and advisory statements for OTC products could be updated to include women who are trying to become pregnant such as:

> *Do not use if trying to become pregnant, or during the first 6 months of pregnancy except on doctor's advice. Do not use at all during the last 3 months of pregnancy.*

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- There is sufficient evidence for an association between NSAIDs included in this review and spontaneous abortion.
- Updates to the data sheets are necessary. If yes, what information should this include? Should these updates be required for eye drop preparations?
- Medsafe should consult on updates to the required warning and advisory statements for NSAID OTC products.
- This requires further communication other than MARC's Remarks in *Prescriber Update.*
- Any other regulatory action is required.

6.0 ANNEXES

1. TGA safety review October 2016

7.0 REFERENCES

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