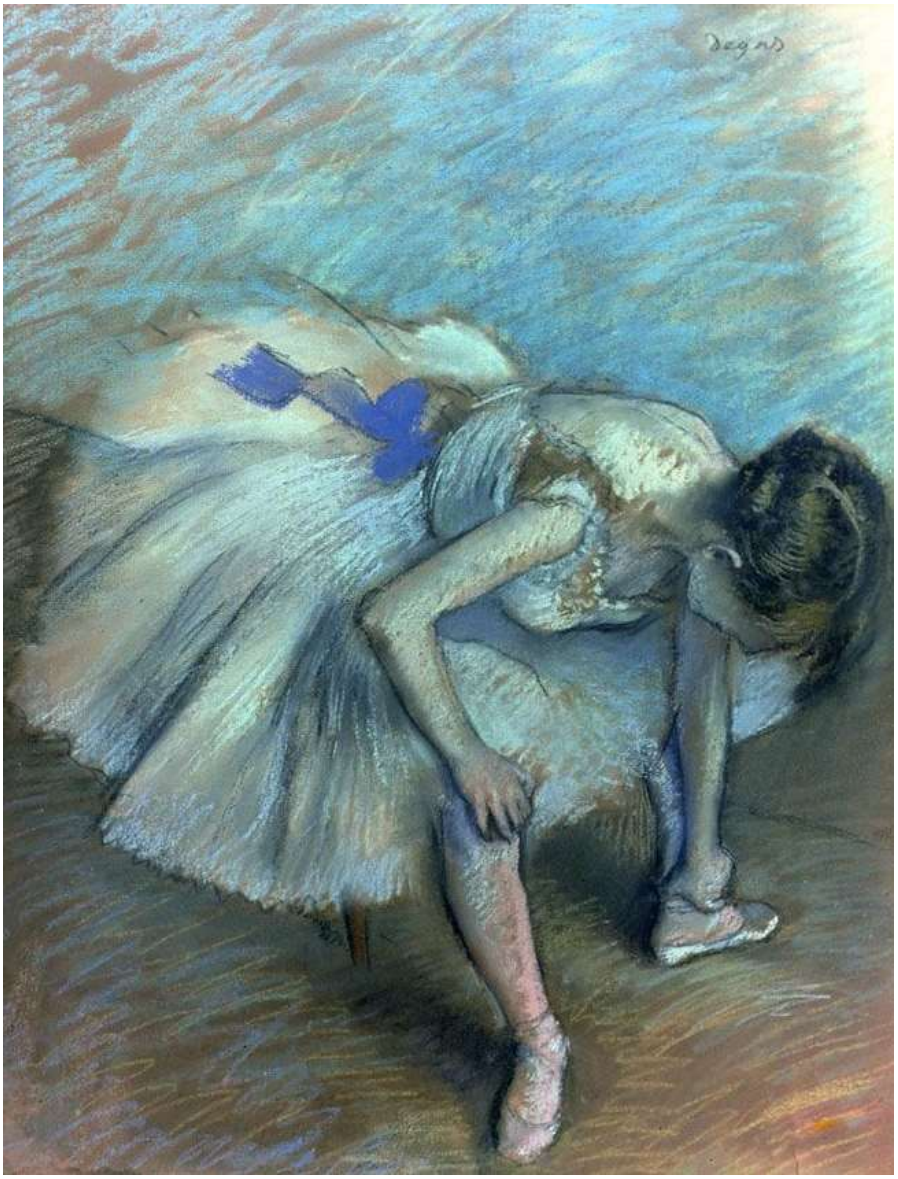
THE NORTHERN HOSPITAL

DICLOFENAC

"The Foyer of the Opera House", oil on canvas, 1872, Edgar Degas.

Edgar Degas' most famous motif was his ballet dancers, though somewhat surprisingly we rarely see them in actual stage performance! Rather we see them in exhausting training routines. Dance masters conduct their classes under the closest of scrutiny, anxious or sometimes indifferent mothers look on in the background. We see them constantly fidgeting with straps and shoes, incessantly adjusting hair or costume. We see them simply preparing for rehearsal or we see them collapsed down on chairs rubbing tired and painful feet. Becoming a famous ballet dancer in the early years of Belle Epoch Paris, was one way in which impoverished young women could hope to advance themselves in society. The rich and powerful flocked to the ballet, where it was prestigious to be seem. Women of good "breeding" would scowl at the amount of leg that was shown by the ballerinas, however the

men, including the husbands of these women, would be greatly attracted. To be noticed by a rich banker, stock broker or wealthy aristocrat, was a strongly motivating benefit every young ballerina, and their mother was acutely aware of. Degas was far more interested in the off-stage life and intrigues of the ballerinas and their rich patrons than he ever was in their actual performances! Artistically he was enthralled by the grace and the movements of the ballerinas, and his fascination was heightened not by any actual performance but rather by the frantic preparations going on behind the scenes. Powerful connections ensured that he held an exclusive pass for entry into the rooms of the dancers and foyers before, during and after the performances, as well as private viewings of training sessions. It was his obsessive observation of the endless and exacting training routines and the frantic last minute preparations before curtain rise which fascinated him, rather than the performance itself. On the few occasions we do see dancers on stage, they are almost incidental, props in the background to the main foreground figures of the interacting audience or the orchestra pits! Perhaps part of Degas' fascination in the dancers' routines, lay in his obsessive and relentless pursuit of perfection in his own works.



In Degas' "The Foyer of the Opera House" we see one such exacting training session. The dance instructor directs the ballerina to contort her feet into the most impossible postures and forced to maintain these for many minutes. Within Degas' ballerina motif, we also see recurring images of dancers resting and massaging their aching feet.

We may sympathize with these young girls and women as NSAIDs did not exist in the early years of La Belle Epoch!

"Seated Dancer", pastel on paper, c.1881-82, Edgar Degas.

DICLOFENAC

Introduction

Diclofenac (trade name in Australia, **Voltaren,** among others) is a widely used non-steroidal anti-inflammatory drug, (**NSAID).**

It is a non-selective inhibitor of cyclooxygenase.

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, are used for their mild to moderate **analgesic** and **anti-inflammatory** effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently prescribed classes of drugs and adverse events related to their use are common.

Although the overall risk of a serious gastrointestinal adverse event such as overt bleeding or perforation is relatively low, there are subsets of patients at much higher risk.

The volume of NSAID use results in a substantial burden of morbidity and mortality, and incurs considerable health care costs.

If NSAIDs are needed, it is best to use the *lowest possible dose* of a *shorter-acting* NSAID for as *short a time* as possible

See also separate Document on NSAID overdose.

History

In 1971, a U.K. research team, headed by **Professor John Vane**, demonstrated that aspirin-like drugs could inhibit the synthesis of prostaglandins.

The biochemists **Sune K. Bergström, Bengt I. Samuelsson** and **John R. Vane** were jointly awarded the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.

Chemistry

Diclofenac belongs to the **hetero-aryl acetic acid group** of NSIADs (which also include **ketorolac**).

Physiology

Cyclo-oxygenase **(or COX)** has 2 forms:

1. COX 1:

    - Generation of PGs involved in GIT mucosal protection.

- Generation of thromboxane within platelets.

2. COX 2:

   - Generation of PGs involved in the inflammatory process.
   - Generation of PGs within the kidney.

NSAIDs may **non-selectively** to inhibit the COX enzyme or may **selectively** inhibit the COX-1 or COX-2 isoforms.

Classification

Accordingly NSAIDS can be classified as:

1. Non-selective COX inhibitors:

   These older agents non-selectively inhibit COX 1 and COX 2.

   By their COX 1 action they have side effects with respect to GIT ulceration and anti-platelet action.

   By their COX 2 action they can have effects on renal function.

   Examples include:

   - Indomethacin
   - Ibuprofen
   - Aspirin
   - **Diclofenac**
   - Ketoprofen
   - Ketorolac
   - Mefenamic acid
   - Naproxen
   - Piroxicam
   - Sulindac

2. Selective COX 2 inhibitors, (also termed coxibs):

These have fewer side effects as COX 1 is not inhibited to a large extent.

They may still have effects on renal function however.

Examples include:

- Celecoxib
- Meloxicam
- Etoricoxib
- Parecoxib

Note that some selective COX-2 inhibitors (such as meloxicam) are only selective at *low doses.*

Cyclo-oxygenase-2 (COX-2) selective NSAIDs reduce, but do not completely abolish, the risk of ulcer disease and complications.

Concomitant aspirin use negates the effect.

Most benefit occurs in those at least risk, with less risk reduction in those most at risk.

Moreover, COX-2 selective NSAIDs do not cause fewer *dyspeptic symptoms* than nonselective NSAIDs.

Their increased relative risk for adverse vascular events has limited the use of COX-2–selective NSAIDs in patients with cardiovascular risk factors.

The relative cardiovascular and cerebrovascular risk of nonselective NSAIDs is under evaluation. At the time of writing, naproxen appears to confer the least cardiovascular risk.

Preparation

Tablets:

- 12.5 mg, 25 mg, 50 mg.

Liquid:

- As powder for reconstitution, 50 mg

Suppositories:

- 12.5mg, 25 mg. 50mg, 50 mg.

Topical Gels:

- 1 % gel.

Ocular topical solution:

- 0.1% (eye drops).

Mechanism of Action

NSAIDs exert their main effect by inhibition of the enzyme **cyclo-oxygenase (or COX)** with consequent reduction in the synthesis of **pro-inflammatory prostaglandins** derived from **arachidonic acid**, **(see Appendix 1 below).**

Inhibition of **COX−2** results in **anti-inflammatory** and **analgesic action**

Reduction in glomerular filtration rate and renal blood flow occurs with both COX−1 and COX−2 inhibition.

Most NSAIDs are non-selective, inhibiting both COX−1 and COX−2. Although selective COX−2 inhibitors have little or no effect on COX−1 at therapeutic doses, they can still be associated with GI adverse effects.

Aspirin irreversibly inhibits cyclo-oxygenase

Other NSAIDS reversibly inhibit cyclo-oxygenase

Pharmacodynamics

Therapeutic clinical effects of the NSAIDS as a class include:

1. Mild to moderate analgesic
2. Anti-inflammatory action.
3. Mild antipyretic

Note that non-selective NSAIDs can have some mild anti-platelet effects but are *unreliable as a therapeutic agent when compared to aspirin.*

The COX 2 inhibitors do not affect platelet activity.

Pharmacokinetics

Absorption:

- Diclofenac can be administered, orally, topically (to skin or eye) or via a suppository.

  Diclofenac is rapidly and almost completely absorbed.

Distribution:

- It is highly but reversibly bound to plasma proteins.

Metabolism and excretion:

- Diclofenac is metabolized in the liver.

Indications

Mild to moderate pain

In common with the NSAIDs as a class, indications include:

1. Tension headache
2. Myalgias in general e.g. associated with infections
3. Soft tissue and musculoskeletal traumatic injury
4. Pleuritc pain
5. Inflammatory conditions:
    - Arthritis, arthralgia, tendonitis, fasciitis
6. Osteoarthritis
7. **Gout**
8. Dysmenorrhoea

Note that no single NSAID has been shown to be more effective than any other, but some patients do seem to respond better to one particular agent than to other agents.

Contraindications/ Precautions

Contraindications and precautions of the NSAIDS as a class include:

1. Renal impairment:

    All NSAIDs can cause renal impairment, especially in:

    - The elderly
    - Those who already have renal impairment

- Those who are taking other nephrotoxic agents.
- Those who are dehydrated (as prostaglandins are important in maintaining renal blood flow when circulating blood volume is decreased).

2. Elderly, (generally > 65 years):
   - The elderly are at more risk of NSAID adverse effects, particularly renal impairment, heart failure, and GI ulceration..
3. Heart failure
   - Due to the sodium and water retaining properties.
4. Hypertension:
   - Due to the sodium and water retaining properties.
5. Gastritis / oesophagitis/ peptic ulcer disease:
   - The risk of GIT side effects is less with the COX-2 selective agents.
6. Known allergy to NSAIDS.
7. Asthma:
   - NSAIDs in general are a well recognized risk factor for asthma.

     If a person with asthma has taken NSAIDs previously without triggering asthma symptoms, the use of NSAIDs on a future occasion is not contraindicated.

Pregnancy

Diclofenac is a class C drug with respect to pregnancy.

Class C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialized texts should be consulted for further details.

The use of non-steroidal anti-inflammatory agents (NSAID) during the first trimester has not been associated with an increased risk of congenital malformations. However, use of NSAID may increase risk of spontaneous abortion, but this has not been conclusively confirmed. Maternal use of NSAID in late pregnancy has been associated with an increased risk of premature closure of the ductus arteriosus, persistent pulmonary hypertension of the newborn, nephrotoxicity and oligohydramnios. Therefore, the use of all oral and topical NSAID preparations (except for low dose aspirin) is not recommended during pregnancy. [5]

Breastfeeding

Is generally considered safe, however, if an NSAID is required in a breastfeeding patient, **diclofenac** or **ibuprofen** is preferred. [1]

Adverse Effects

Adverse effects of the NSAIDS as a class include:

1. Exacerbation of CCF

2. Exacerbation of hypertension

3. CVS events:

    - There is some evidence that cardiovascular harm (**stroke/ ACS**) is a general adverse effect of NSAIDs **other than aspirin. This risk is greatest with the selective COX 2 inhibitors, (see also Appendix 3 below).**

    - Low-dose aspirin may reduce the increased cardiovascular risk associated with NSAIDs, but it will increase gastrointestinal adverse effects.

4. GIT upset:

    - Nausea/ dyspepsia

    - Inflammation/ erosions/ ulceration:

      With the secondary complications of dyspepsia, GIT bleeding or perforation.

      Upper abdominal pain or discomfort has been reported in up to a half of NSAID users, but symptom analysis cannot reliably distinguish between NSAID-related dyspepsia and pain due to peptic ulceration.

      About 15% to 30% of NSAID users have ulcers visible at endoscopy, but many of them are asymptomatic until complications such as anaemia, bleeding or perforation occur

      Over-the-counter NSAIDs may also cause dyspeptic symptoms, but their risk of causing ulcer and bleeding appears to be lower than for **prescribed** NSAIDs, because of their lower dose, shorter half-life and generally shorter duration of use. [2]

      The **Patient Risk factors** for NSAID-induced upper gastrointestinal bleeding or perforation are as follows, (in order of risk):

      ♥ **Older age**

- ♥ Past history of upper gastrointestinal bleeding
- ♥ Past history of peptic ulcer disease
- ♥ *Helicobacter pylori* infection
- ♥ Concomitant drugs, including (in order of risk) anticoagulants, antiplatelet drugs, SSRIs and corticosteroids
- ♥ Significant co-morbidity
- ♥ Smoking
- ♥ Excessive alcohol intake

Specific **NSAID risk factors** include:

- ♥ Higher doses
- ♥ Long duration of use:
  - ♥♥ The risk of ulcer is higher with longer-acting NSAIDs such as piroxicam and ketoprofen, than with shorter-acting agents such as ibuprofen and diclofenac.

5. Renal impairment:

Especially in:

- Elderly
- Those with pre-existing renal impairment
- Dehydration

NSAIDs, in general have been associated with acute interstitial nephritis with haematuria, proteinuria and, occasionally, nephrotic syndrome.

6. Allergic reactions.

- **Allergic type reactions are relatively common with the NSAIDs as a class.**

  NSAIDs, in general can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal and may occur without

warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use.

7. Bleeding:

- **Aspirin** produces the strongest effect in this regard via its irreversible effect on COX.

  All other **non-selective** NSAIDs may *slightly* increase risk of bleeding via an antiplatelet effect mediated by COX 1 inhibition.

  The COX 2 inhibitors do not affect platelet activity.

Rarely:

8 Hepatotoxicity

9 Blood dyscracias

Dosing

Exact dosing regimens can depend on the condition being treated as well as its severity.

In general terms:

Adults:

- Orally: 75 - 150 mg daily in 2 or 3 doses. Maximum daily dose is 200 mg.

  Rectally: 75 - 150 mg daily in 2 or 3 doses. Maximum daily dose is 200 mg.

Children (over 12 months):

- Child: Oral: 0.5 - 1 mg/kg (maximum 50 mg) 2 or 3 times daily.

  Rectal: 0.5 - 1 mg/kg (maximum 50 mg) 2 or 3 times daily.

  Use 1- 1.5 mg/kg (maximum 75 mg) twice daily in juvenile idiopathic arthritis; total daily dose may be given in 3 doses

Topical (skin):

- 1% gel, rub into the affected area 3 or 4 times daily.

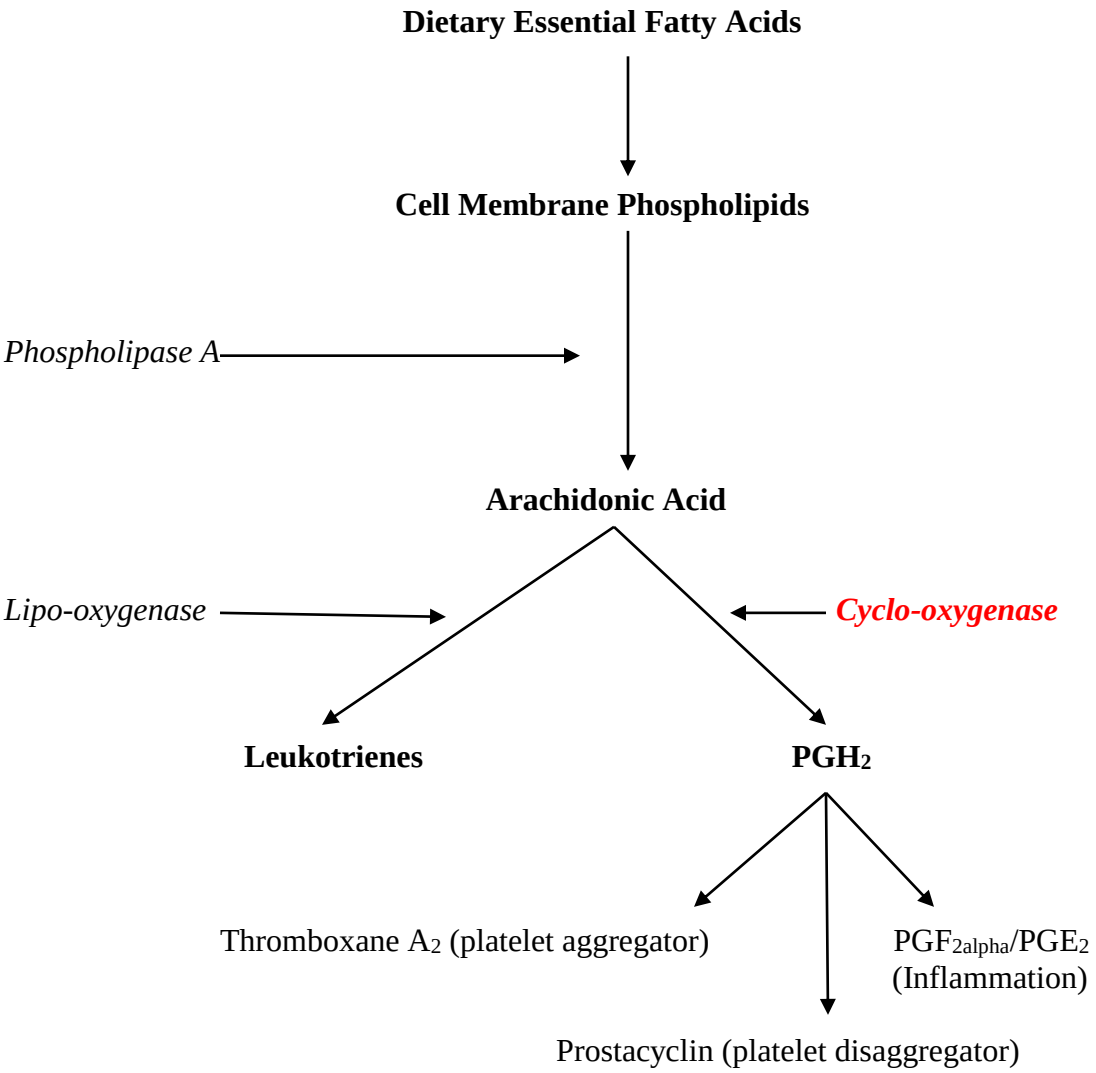
Ocular drops:

- Ocular diclofenac 0.1% eye drops, 1 drop 4 - 6 hourly [4]

See also Appendix 2 below for further prescribing considerations.

Appendix 1

NSAID Action



Platelet aggregation will depend on the ratio:

Prostacyclin
Thromboxane A_2

Aspirin irreversibly inhibits cyclo-oxygenase.

Other NSAIDS reversibly inhibit cyclo-oxygenase

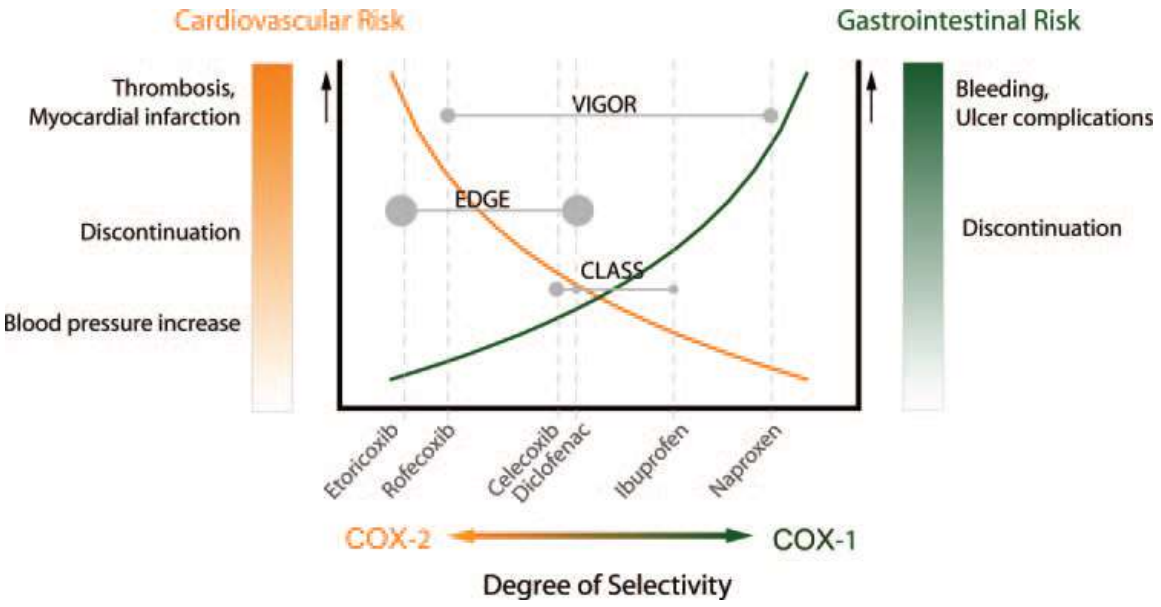
Appendix 2

Considerations in prescribing NSAIDs:

Important points to consider when prescribing Nonsteroidal anti-inflammatory drugs (NSAIDs) include: [2]

- Consider nonpharmacological treatment if appropriate.
- Consider the harm- benefit profile for NSAIDs in each patient and encourage patients to address modifiable cardiovascular risk factors.
- Use the minimal effective dose for the shortest time possible.
- Consider using alternatives such as fish oils or paracetamol to reduce the need for NSAIDs.
- Consider testing for *Helicobacter pylori* infection and treat if present.
- Choose an NSAID with a short half-life for use in the older patient and in patients with renal impairment.
- Use topical NSAIDs where appropriate.
- Use NSAIDs with low risk of gastrointestinal complications (eg ibuprofen, diclofenac).
- Use only one non-aspirin NSAID at a time.
- Monitor by assessing both adverse effects and the need for NSAID use.
- Co-prescription of a **proton pump inhibitor.**

Appendix 3



Increasing degrees of selectivity for COX-2 are associated with augmented cardiovascular risk, whereas increasing degrees of selectivity for COX-1 are associated with augmented GI risk, (From Elliott M. Antman et al. Use of Nonsteroidal Anti-inflammatory Drugs, An Update for Clinicians, A Scientific Statement From the American Heart Association. Circulation. 2007;115:1634-1642).(Vigor, Edge, Class refer to various clinical trials).

References

1. eTG Complete - March 2015

    - GIT Therapeutic Guidelines, 5th ed 2011

2. Diclofenac in Australian Medicines Handbook Website, Accessed May 2015.

3. Diclofenac in MIMs 1 July 2013.

4. Eye Emergency Manual NSW Department of Health, 2nd ed May 2009.

5. RWH Pregnancy & Breastfeeding Guidelines, 25 February 2015.

Dr J. Hayes
Reviewed April 2017.