29.1 GENERAL PRINCIPLES

- Non-steroidal anti-inflammatory drugs (NSAIDs) consist of a heterogenous group of compounds that can be subdivided by virtue of their pharmacology: ¹
  - Non-selective NSAIDs inhibit both COX-1 and COX-2 receptors e.g. ibuprofen, naproxen.
  - COX-2 selective NSAIDs display some selectivity for COX-2 receptors but this diminishes as the dose increases e.g. etodolac, meloxicam.
  - COX-2 inhibitors specifically inhibit COX-2 receptors at therapeutic doses whilst being COX-1 sparing e.g. celecoxib, etoricoxib.
- All NSAIDs have significant cardiovascular and gastrointestinal toxicity. ²
- Consider whether alternative treatment would be appropriate (e.g. topical NSAIDs, paracetamol, tramadol). ¹
- Prescribe the lowest effective dose of NSAID for the shortest time necessary. ³

29.2 GUIDELINES

29.2.1 Cardiovascular risk and NSAID prescribing

- COX-2 inhibitors are contraindicated for use in patients with established ischaemic heart disease and / or cerebrovascular disease, and also in patients with peripheral arterial disease. ⁴ [Level 1]
- Despite conflicting evidence, non-selective NSAIDs and COX-2 selective NSAIDs are currently licensed for use in these groups of patients, although they should be used with caution. ¹ [Level 4]

29.2.2 Renal dysfunction and NSAID prescribing

- Renal function should be assessed prior to the introduction of a NSAID and within 7 days of starting treatment or increasing the dose. ⁵, ⁶ [Level 4]
- Care is required when prescribing NSAIDs for patients with heart failure, ascites or impaired renal function, particularly those who are dehydrated or have a low effective circulating volume. ⁵, ⁶ [Level 4]
- Long term administration of NSAIDs has been linked to papillary necrosis and other renal injuries. Patients with impaired renal function, heart failure, liver dysfunction, the elderly and those taking diuretics and / or angiotensin-converting enzyme inhibitors are at greatest risk from this reaction. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state. ⁷ [Level 4]
- Use of NSAIDs in patients with advanced renal disease is not recommended due to a lack of safety data from controlled clinical studies. If NSAIDs are prescribed it is essential that renal function is monitored closely. ⁵, ⁶ [Level 4]
29.2.3  Gastrointestinal toxicity

- Patients at high risk of gastrointestinal side effects from NSAIDs include the following: [8, 9] [Level 4]
  - Elderly (age >65 years). The risk increases with age.
  - Previous upper gastroduodenal perforation, ulcers and bleeds.
  - Concurrent use of aspirin, warfarin, corticosteroids or selective serotonin reuptake inhibitors (SSRIs).
  - Patients receiving maximum doses of NSAIDs.

- Undesirable gastric side effects from celecoxib are significantly less than from non-selective NSAIDs although it is not clear whether this lower risk continues with long term use. [10] [Level 4]

- In patients taking clopidogrel, it is advisable to use an H₂ antagonist at a higher dose than usual e.g. ranitidine 300mg bd. [19] [Level 4]

29.2.4  Proton Pump Inhibitors

- A proton pump inhibitor (PPI) should be co-prescribed with a NSAID, regardless of which actual drug is chosen. [1] [Level 4] This is cost effective in the treatment of osteoarthritis, but the benefit of a PPI with a COX-2 inhibitor in other situations is unclear. [11] [Level 4]

- The relationship between H. pylori infection and NSAIDs in gastroduodenal pathology is complex. Eradication of H. pylori infection may prevent peptic ulcer disease in patients who are naïve users of NSAIDs. Patients receiving long term PPI treatment for prevention of NSAID ulcers should be tested for H. pylori. Eradication of H. pylori will reduce the risk of accelerated loss of specialised glands and atrophic gastritis. [12] [Level 4]

- Appropriate proton pump inhibitors and oral doses include: [15] [Level 4]
  - Esomeprazole 20mg od.
  - Lansoprazole 30mg od.
  - Omeprazole 20mg od.
  - Pantoprazole 40mg od.

- Misoprostol is a synthetic prostaglandin analogue with gastric anti-secretory and protective properties which can be used to protect against NSAID-induced gastrointestinal damage. It is more effective than PPIs but can be poorly tolerated. Side effects include colic and diarrhoea. A suggested starting dose is 200micrograms od, increasing by 200 micrograms every 1-2 days to a normal dose of 200micrograms qds. [17, 18] [Level 1]
29.2.5 **Choice of NSAID**

- Before deciding which NSAID to use, the prescriber must first assess patient risk factors for cardiovascular and gastrointestinal toxicity (see Figure 29.1). ¹, ², ³ [Level 4]
- Table 29.1 lists NSAIDs currently recommended for use; Table 29.2 lists additional NSAIDs that may be considered second line options. ¹ [Level 4]

29.2.6 **Monitoring Effectiveness**

- NSAIDs should be prescribed for at least 7 days before reviewing their clinical effectiveness. The analgesic effect of the drug becomes apparent within the first few days of treatment. The anti-inflammatory response may take at least 2 weeks to become evident. ⁸ [Level 4]
- It may be appropriate to use an alternative NSAID before concluding that NSAIDs are ineffective. ⁸ [Level 4]
- Due to the increased risk of renal and gastroduodenal toxicity, ketorolac should only be used for refractory pain (see Table 29.2). A PPI should always be co-prescribed with ketorolac unless the patient is in the dying phase. ⁸ [Level 4]

29.3 **STANDARDS**

1. COX-2 inhibitors are contra-indicated for use in patients with existing ischaemic heart disease, peripheral vascular disease or cerebrovascular disease. ⁴, ¹³ [Grade B]
2. In patients with existing cardiovascular disease, alternative analgesia should be considered before introducing a non-selective NSAID or a COX-2 selective NSAID (e.g. paracetamol, tramadol, topical NSAID). If NSAIDs are to be used, the lowest dose possible should be prescribed and the patient should be reviewed within 7 days.³ [Grade D]
3. It may be appropriate to use an alternative NSAID before concluding that NSAIDs are ineffective. ⁸ [Grade D]
4. Patients with risk factors for gastrointestinal toxicity should be prescribed proton pump inhibitors or misoprostol for gastric protection. ¹⁴, ¹⁷, ¹⁸ [Grade B]
5. A PPI should be prescribed for all patients receiving subcutaneous NSAIDs, unless they are in the dying phase. ⁸ [Grade D]
6. Renal function should be assessed prior to the introduction of a NSAID and within 7 days of starting treatment or increasing the dose. ⁵, ⁶ [Grade D]
### Table 29.1  
**NSAIDs currently recommended for use**  
[Level 4]

<table>
<thead>
<tr>
<th>Class of NSAID</th>
<th>Name of drug</th>
<th>Oral dose</th>
<th>CSCI over 24 hours</th>
<th>Additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non selective</td>
<td>Naproxen</td>
<td>500mg bd</td>
<td>n/a</td>
<td>Suitable 1st line choice, together with PPI for patients with CV risk.</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>400mg-800mg tds</td>
<td>n/a</td>
<td>Low dose ibuprofen (≤1200mg) suitable 1st line choice, together with PPI, for patients with CV risk. If low dose aspirin is co-prescribed, ibuprofen should be given at least 8 hours before or 30 minutes afterwards. Alternatively, change aspirin to clopidogrel.</td>
</tr>
<tr>
<td>COX-2 inhibitor</td>
<td>Celecoxib</td>
<td>100mg-200mg bd</td>
<td>n/a</td>
<td>Suitable 1st line choice in patients at high risk of GI toxicity and low CV risk. PPI should be co-prescribed in high GI risk patients.</td>
</tr>
</tbody>
</table>

### Table 29.2  
**Additional NSAIDs available for use**  
[Level 4]

<table>
<thead>
<tr>
<th>Class of NSAID</th>
<th>Name of drug</th>
<th>Oral dose</th>
<th>CSCI over 24 hours</th>
<th>Additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non selective</td>
<td>Diclofenac sodium</td>
<td>50mg tds</td>
<td>Painful. Dose 150mg daily</td>
<td>150mg daily via rectal route. Diclofenac is associated with similar thrombotic risk to COX-2 inhibitors.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75mg n/r bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nabumetone</td>
<td>500mg od-1g bd</td>
<td>n/a</td>
<td>Lowest GI risk of all non-selective NSAIDs. Some units may use first line.</td>
</tr>
<tr>
<td></td>
<td>Ketorolac</td>
<td>n/a</td>
<td>30mg-90mg</td>
<td>Can give 10mg stat subcutaneous dose. Carries greater risk of renal and gastrointestinal toxicity compared to other NSAIDs. Due to the propensity for toxicity, the continued need for a CSCI of ketorolac should be reviewed on a weekly basis.</td>
</tr>
<tr>
<td></td>
<td>Piroxicam melt</td>
<td>20mg od (sublingual)</td>
<td></td>
<td>Increased risk of GI toxicity and serious skin reactions. Not to be used for first line treatment.</td>
</tr>
<tr>
<td>COX-2 selective</td>
<td>Etodolac</td>
<td>600mg m/r od</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2 inhibitor</td>
<td>Etoricoxib</td>
<td>60mg-120mg od</td>
<td></td>
<td>NICE do not recommend etoricoxib for first line use in osteoarthritis. For this reason, consider as 2nd line choice.</td>
</tr>
</tbody>
</table>
Consider whether alternative treatment would be appropriate

Assessment of cardiovascular (CV) history

No CV History
- Assessment of gastrointestinal (GI) risk factors
  - Low GI risk: See LIST A
  - ≥1 GI risk: See LIST B

CV History
- Assessment of gastrointestinal (GI) risk factors
  - Low GI risk: See LIST C
  - ≥1 GI risk: See LIST D
### Table 29.3 Choice of NSAID available, according to cardiovascular history and gastrointestinal risk factors. [Level 4]

<table>
<thead>
<tr>
<th>Step</th>
<th>LIST A</th>
<th>LIST B</th>
<th>LIST C</th>
<th>LIST D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No CV history</td>
<td>No CV history</td>
<td>CV history</td>
<td>CV history</td>
</tr>
<tr>
<td></td>
<td>No GI risk</td>
<td>GI risk</td>
<td>No GI risk</td>
<td>GI risk</td>
</tr>
<tr>
<td>1</td>
<td>Alternative analgesia</td>
<td>Alternative analgesia</td>
<td>Alternative analgesia</td>
<td>Alternative analgesia</td>
</tr>
<tr>
<td></td>
<td>e.g. topical NSAID, paracetamol, tramadol.</td>
<td>e.g. topical NSAID, paracetamol, tramadol.</td>
<td>e.g. topical NSAID, paracetamol, tramadol.</td>
<td>e.g. topical NSAID, paracetamol, tramadol.</td>
</tr>
<tr>
<td>2</td>
<td>Low dose ibuprofen (≤1200mg/day) + PPI or nabumetone + PPI</td>
<td>COX-2 Inhibitor e.g. celecoxib + PPI</td>
<td>Low dose ibuprofen (≤1200mg/day) + PPI or naproxen + PPI</td>
<td>Low dose ibuprofen (≤1200mg/day) + PPI or naproxen + PPI</td>
</tr>
<tr>
<td>3</td>
<td>Non-selective NSAID e.g. diclofenac + PPI or naproxen + PPI</td>
<td>COX-2 Inhibitor e.g. etoricoxib + PPI</td>
<td>Non-selective NSAID e.g. nabumetone + PPI</td>
<td>Non-selective NSAID e.g. nabumetone + PPI</td>
</tr>
<tr>
<td>4</td>
<td>COX-2 selective NSAID e.g. etodolac + PPI</td>
<td>Low dose ibuprofen (&lt;1200mg/day) + PPI or nabumetone + PPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>COX-2 inhibitor e.g. celecoxib</td>
<td>COX-2 selective NSAID e.g. etodolac + PPI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Misoprostol can be considered as an alternative to a PPI

### 29.4 REFERENCES


29.5 **CONTRIBUTORS**

**Lead Contributors**

Mr A Dickman  
Specialist Principal Pharmacist  
Marie Curie Palliative Care Institute  
Liverpool

Dr J Bellieu  
Specialist Registrar in Palliative Medicine  
Marie Curie Hospice  
Liverpool

Dr M Makin  
Chief of Staff (Cancer Services)  
Consultant and Visiting Professor in Palliative Medicine  
Betsi Cadwaladr University Health Board and Glyndwr University  
Wales

**External Reviewer**

Dr V Pace  
Consultant in Palliative Medicine  
St Christopher’s Hospice  
London