**Osteoarthritis and soft-tissue disorders**

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* [Previous](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/rheumatoid-arthritis-and-other-inflammatory-disorders)
* [Next](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs)

For pain relief in osteoarthritis and soft-tissue disorders, **paracetamol** ([section 4.7.1](http://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/47-analgesics/471-non-opioid-analgesics-and-compound-analgesic-preparations%22%20%5Co%20%22Non-opioid%20analgesics%20and%20compound%20analgesic%20preparations%20%28Central%20nervous%20system%29)) should be used first and may need to be taken regularly. A **topical NSAID** ([section 10.3.2](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/103-drugs-for-the-treatment-of-soft-tissue-disorders-and-topical-pain-relief/1032-rubefacients-topical-nsaids-capsaicin-and-poultices%22%20%5Co%20%22Rubefacients%2C%20topical%20NSAIDs%2C%20capsaicin%2C%20and%20poultices%20%28Musculoskeletal%20and%20joint%20diseases%29)) or topical **capsaicin** 0.025% ([section 10.3.2](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/103-drugs-for-the-treatment-of-soft-tissue-disorders-and-topical-pain-relief/1032-rubefacients-topical-nsaids-capsaicin-and-poultices%22%20%5Co%20%22Rubefacients%2C%20topical%20NSAIDs%2C%20capsaicin%2C%20and%20poultices%20%28Musculoskeletal%20and%20joint%20diseases%29)) should also be considered, particularly in knee or hand osteoarthritis. An **oral NSAID** ([section 10.1.1](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs)) can be substituted for, or used in addition to, paracetamol. If further pain relief is required in osteoarthritis, then the addition of an **opioid** analgesic ([section 4.7.2](http://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/47-analgesics/472-opioid-analgesics)) may be considered, but with a substantial risk of adverse effects; however, an opioid analgesic should be considered before a NSAID in patients taking low-dose aspirin. For advice on the prophylaxis and treatment of NSAID-associated gastro-intestinal ulcers, see [section 1.3](http://www.evidence.nhs.uk/formulary/bnf/current/1-gastro-intestinal-system/13-antisecretory-drugs-and-mucosal-protectants/nsaid-associated-ulcers).

Intra-articular **corticosteroid** injections ([section 10.1.2.2](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1012-corticosteroids/10122-local-corticosteroid-injections)) may produce temporary benefit in osteoarthritis, especially if associated with soft-tissue inflammation.

Non-drug measures, such as weight reduction and exercise, should also be encouraged.

**Glucosamine** ([section 10.1.5](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1015-other-drugs-for-rheumatic-diseases/glucosamine)) and **rubefacients** (section [10.3.2](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/103-drugs-for-the-treatment-of-soft-tissue-disorders-and-topical-pain-relief/1032-rubefacients-topical-nsaids-capsaicin-and-poultices)) are not recommended for the treatment of osteoarthritis.

**Hyaluronic acid** and its derivatives are available for osteoarthritis of the knee, but are not recommended. Sodium hyaluronate (*Durolane*®, *Euflexxa*®, *Fermathron*®, *Hyalgan*®, *Orthovisc*®, *Ostenil*®, *Ostenil Plus*®, *RenehaVis*®, *Suplasyn*®, *Synocrom*®, *Synopsis*®) or hylan G-F 20 (*Synvisc*®) is injected intra-articularly to supplement natural hyaluronic acid in the synovial fluid. These injections may reduce pain over 1–6 months, but are associated with a short-term increase in knee inflammation. Sodium hyaluronate (*SportVis*®) is also licensed for the relief of pain and optimisation of recovery following ankle sprain, and for the relief of chronic pain and disability associated with tennis elbow.

# 10.1.1 Non-steroidal anti-inflammatory drugs

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* [Previous](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/osteoarthritis-and-soft-tissue-disorders)
* [Next](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs/aceclofenac)

Additional information interactions ([NSAIDs](http://www.evidence.nhs.uk/formulary/bnf/current/a1-interactions/list-of-drug-interactions/analgesics/nsaids%22%20%5Co%20%22NSAIDs)).

In single doses non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic activity comparable to that of paracetamol ([section 4.7.1](http://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/47-analgesics/471-non-opioid-analgesics-and-compound-analgesic-preparations)), but paracetamol is preferred, particularly in the elderly (see also [Prescribing for the Elderly](http://www.evidence.nhs.uk/formulary/bnf/current/guidance-on-prescribing/prescribing-for-the-elderly/adverse-reactions#PHP142)).

In regular full dosage NSAIDs have both a lasting analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation. Therefore, although paracetamol often gives adequate pain control in osteoarthritis, NSAIDs are more appropriate than paracetamol or the opioid analgesics in the inflammatory arthritides (e.g. rheumatoid arthritis) and in some cases of advanced osteoarthritis. NSAIDs can also be of benefit in the less well defined conditions of back pain and soft-tissue disorders.

## Choice

Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individual response and tolerance to these drugs. About 60% of patients will respond to any NSAID; of the others, those who do not respond to one may well respond to another. Pain relief starts soon after taking the first dose and a full analgesic effect should normally be obtained within a week, whereas an anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to 3 weeks. If appropriate responses are not obtained within these times, another NSAID should be tried.

NSAIDs reduce the production of prostaglandins by inhibiting the enzyme cyclo-oxygenase. They vary in their selectivity for inhibiting different types of cyclo-oxygenase; selective inhibition of cyclo-oxygenase-2 is associated with less gastro-intestinal intolerance. Several other factors also influence susceptibility to gastro-intestinal effects, and a NSAID should be chosen on the basis of the incidence of gastro-intestinal and other side-effects.

**Ibuprofen** is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other non-selective NSAIDs but its anti-inflammatory properties are weaker. Doses of 1.6 to 2.4 g daily are needed for rheumatoid arthritis and it is unsuitable for conditions where inflammation is prominent, such as acute gout. **Dexibuprofen** is the active enantiomer of ibuprofen. It has similar properties to ibuprofen and is licensed for the relief of mild to moderate pain and inflammation.

Other propionic acid derivatives:

**Naproxen** is one of the first choices because it combines good efficacy with a low incidence of side-effects (but more than ibuprofen, see [NSAIDs and Gastro-intestinal Events](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6403), below).

**Fenoprofen** is as effective as naproxen, and **flurbiprofen** may be slightly more effective. Both are associated with slightly more gastro-intestinal side-effects than ibuprofen.

**Ketoprofen** has anti-inflammatory properties similar to ibuprofen and has more side-effects (see also [NSAIDs and Gastro-intestinal Events](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6403), below). **Dexketoprofen**, an isomer of ketoprofen, has been introduced for the short-term relief of mild to moderate pain.

**Tiaprofenic acid** is as effective as naproxen; it has more side-effects than ibuprofen (**important:** reports of severe cystitis, see CSM advice under [Tiaprofenic acid](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs/tiaprofenic-acid#PHP6521)).

Drugs with properties similar to those of propionic acid derivatives:

**Diclofenac** and **aceclofenac** are similar in efficacy to naproxen.

**Etodolac** is comparable in efficacy to naproxen; it is licensed for symptomatic relief of osteoarthritis and rheumatoid arthritis.

**Indometacin** has an action equal to or superior to that of naproxen, but with a high incidence of side-effects including headache, dizziness, and gastro-intestinal disturbances (see also [NSAIDs and Gastro-intestinal Events](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6403), below).

**Mefenamic acid** has minor anti-inflammatory properties. It has occasionally been associated with diarrhoea and haemolytic anaemia which require discontinuation of treatment.

**Meloxicam** is licensed for the short-term relief of pain in osteoarthritis and for long-term treatment of rheumatoid arthritis and ankylosing spondylitis.

**Nabumetone** is comparable in effect to naproxen.

**Phenylbutazone** is licensed for ankylosing spondylitis, but is not recommended because it is associated with serious side-effects, in particular haematological reactions; it should be used only by a specialist in severe cases where other treatments have been found unsuitable.

**Piroxicam** is as effective as naproxen and has a long duration of action which permits once-daily administration. However, it has more gastro-intestinal side-effects than most other NSAIDs, and is associated with more frequent serious skin reactions (**important:** see [CHMP advice](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs/piroxicam#PHP6509)).

**Sulindac** is similar in tolerance to naproxen.

**Tenoxicam** is similar in activity and tolerance to naproxen. Its long duration of action allows once-daily administration.

**Tolfenamic acid** is licensed for the treatment of migraine ([section 4.7.4.1](http://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/47-analgesics/474-antimigraine-drugs/4741-treatment-of-acute-migraine)).

**Ketorolac** and the selective inhibitor of cyclo-oxygenase-2, **parecoxib**, are licensed for the short-term management of postoperative pain ([section 15.1.4.2](http://www.evidence.nhs.uk/formulary/bnf/current/15-anaesthesia/151-general-anaesthesia/1514-sedative-and-analgesic-peri-operative-drugs/15142-non-opioid-analgesics)).

The selective inhibitors of cyclo-oxygenase-2, **etoricoxib** and **celecoxib**, are as effective as non-selective NSAIDs such as diclofenac and naproxen. Although selective inhibitors can cause serious gastro-intestinal events, available evidence appears to indicate that the risk of serious upper gastro-intestinal events is lower with selective inhibitors compared to non-selective NSAIDs; this advantage may be lost in patients who require concomitant low-dose aspirin.

**Celecoxib** and **etoricoxib** are licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; etoricoxib is also licensed for the relief of pain from acute gout.

## Dental and orofacial pain

Most mild to moderate dental pain and inflammation is effectively relieved by NSAIDs. Those used for dental pain include **ibuprofen** and **diclofenac**.

For information on the risks of serious gastro-intestinal side-effects of NSAIDs, see [NSAIDs and Gastro-intestinal Events](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6403).

For further information on the management of dental and orofacial pain, see [section 4.7](http://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/47-analgesics#PHP2590).

## Cautions and contra-indications

NSAIDs should be used with caution in the elderly (risk of serious side-effects and fatalities, see also [Prescribing for the Elderly](http://www.evidence.nhs.uk/formulary/bnf/current/guidance-on-prescribing/prescribing-for-the-elderly/adverse-reactions#PHP142) ), in allergic disorders (they are **contra-indicated** in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID), and in coagulation defects. Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment. Caution is also required in patients with connective-tissue disorders, see Side-effects [below](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6402).

In patients with cardiac impairment, caution is required since NSAIDs may impair renal function (see also Side-effects, [below](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6402)). All NSAIDs are contra-indicated in severe heart failure. High-dose **ibuprofen** (≥ 2.4 g daily) and **dexibuprofen** (≥ 1.2 g daily) are contra-indicated in uncontrolled hypertension. **Diclofenac**, **aceclofenac**, **ibuprofen** (≥ 2.4 g daily), **dexibuprofen** (≥ 1.2 g daily) and the selective inhibitors of cyclo-oxygenase-2 (**celecoxib,** **etoricoxib,** and **parecoxib**) are contra-indicated in ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and mild to severe heart failure. They should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, in patients with oedema for any other reason, and in patients with other risk factors for cardiovascular events. Other non-selective NSAIDs should be used with caution in uncontrolled hypertension, heart failure, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, and when used long term in patients with risk factors for cardiovascular events.

#### NSAIDs and cardiovascular events

All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term.

**Cyclo-oxygenase-2 selective inhibitors**, **diclofenac** (150 mg daily) and **ibuprofen** (2.4 g daily) are associated with an increased risk of thrombotic events. Although there are limited data regarding the thrombotic effects of **aceclofenac**, treatment advice has been updated in line with diclofenac, based on aceclofenac's structural similarity to diclofenac and its metabolism to diclofenac. The increased risk for diclofenac is similar to that of licensed doses of **etoricoxib**. **Naproxen** (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of myocardial infarction.

The lowest effective dose of NSAID should be prescribed for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.

All NSAIDs (including cyclo-oxygenase-2 selective inhibitors) are contra-indicated in patients with active gastro-intestinal ulceration or bleeding. Piroxicam, ketoprofen, and ketorolac are contra-indicated in patients with any history of gastro-intestinal bleeding, ulceration, or perforation. Other non-selective NSAIDs are contra-indicated in patients with a history of recurrent gastro-intestinal ulceration or haemorrhage (two or more distinct episodes), and in patients with a history of gastro-intestinal bleeding or perforation related to previous NSAID therapy (see also [NSAIDS and Gastro-intestinal Events](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6403)). While it is preferable to avoid NSAIDs in patients with active or previous gastro-intestinal ulceration or bleeding, and to withdraw them if gastro-intestinal lesions develop, nevertheless patients with serious rheumatic diseases (e.g. rheumatoid arthritis) are usually dependent on NSAIDs for effective relief of pain and stiffness. Patients at risk of gastro-intestinal ulceration (including the elderly), who need NSAID treatment should receive gastroprotective treatment; for advice on the prophylaxis and treatment of NSAID-associated gastro-intestinal ulcers, see [section 1.3](http://www.evidence.nhs.uk/formulary/bnf/current/1-gastro-intestinal-system/13-antisecretory-drugs-and-mucosal-protectants). NSAIDs should also be used with caution in Crohn's disease or ulcerative colitis, as these conditions may be exacerbated.

For **interactions** of NSAIDs, see Appendix 1 (NSAIDs).

## Hepatic impairment

NSAIDs should be used with caution in patients with hepatic impairment; there is an increased risk of gastro-intestinal bleeding and fluid retention. NSAIDs should be avoided in severe liver disease; see also individual drugs.

## Renal impairment

NSAIDs should be avoided if possible or used with caution in patients with renal impairment; the **lowest effective dose** should be used for the **shortest possible duration**, and renal function should be **monitored**. Sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure; deterioration in renal function has also been reported after topical use; see also individual drugs.

## Pregnancy

Most manufacturers advise avoiding the use of NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs the risk. NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labour may be delayed and its duration may be increased. See also individual monographs for [celecoxib](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs/celecoxib%22%20%5Co%20%22CELECOXIB%20%28Musculoskeletal%20and%20joint%20diseases%29) and [etoricoxib](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs/etoricoxib%22%20%5Co%20%22ETORICOXIB%20%28Musculoskeletal%20and%20joint%20diseases%29).

## Breast-feeding

NSAIDs should be used with caution during breast-feeding; see also individual drugs.

## Side-effects

Gastro-intestinal disturbances including discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration occur (see also NSAIDs and Gastro-intestinal Events, below and [Cautions](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6382) above). Systemic as well as local effects of NSAIDs contribute to gastro-intestinal damage; taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration may only partially reduce symptoms such as dyspepsia.

#### NSAIDs and gastro-intestinal events

All NSAIDs are associated with serious gastro-intestinal toxicity; the risk is higher in the elderly. Evidence on the relative safety of non-selective NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam (see also [CHMP advice](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs/piroxicam#PHP6509)), ketoprofen, and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk). **Selective inhibitors of cyclo-oxygenase-2** are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs.

Recommendations are that NSAIDs associated with a low risk e.g. ibuprofen are generally preferred, to start at the lowest recommended dose and not to use more than one oral NSAID at a time. See also [Cautions and Contra-indications](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs%22%20%5Cl%20%22PHP6396%22%20%5Co%20%22Gastro-intestinal%20disorders%20%28NSAIDs%29).

The combination of a NSAID and low-dose aspirin can increase the risk of gastro-intestinal side-effects; this combination should be used only if absolutely necessary and the patient should be monitored closely.

Other side-effects include hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm—see below), headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity, and haematuria. Blood disorders have also occurred. Fluid retention may occur (rarely precipitating congestive heart failure); blood pressure may be raised.

#### Asthma

Any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter.

Renal failure may be provoked by NSAIDs, especially in patients with pre-existing renal impairment (**important**, see [Renal impairment](http://www.evidence.nhs.uk/formulary/bnf/current/10-musculoskeletal-and-joint-diseases/101-drugs-used-in-rheumatic-diseases-and-gout/1011-non-steroidal-anti-inflammatory-drugs#PHP6399), above). Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs can lead to renal failure.

Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare side-effects. Induction of or exacerbation of colitis or Crohn's disease has been reported. Aseptic meningitis has been reported rarely with NSAIDs—patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible.

**Overdosage:** see Emergency Treatment of Poisoning, [Analgesics, non-opioid](http://www.evidence.nhs.uk/formulary/bnf/current/emergency-treatment-of-poisoning/specific-drugs/analgesics-non-opioid#PHP190).