Class: Non-opioid analgesic, NSAID, preferential COX-2 inhibitor.

Indications: Pain in osteo-arthritis and rheumatoid arthritis, †cancer pain.

Contra-indications: Hypersensitivity to aspirin or other NSAID (urticaria, rhinitis, asthma, angioedema), severe liver impairment.

Pharmacology

World-wide, nabumetone is one of the most commonly prescribed NSAIDs. It is a unique NSAID in that it is both a pro-drug and non-acidic. Absorption is mainly unaffected by food, and is increased if taken with milk. It undergoes rapid and extensive first-pass metabolism in the liver to mainly 6-methoxy-2-naphthylacetic acid (6-MNA), which is further metabolized by O-methylation and conjugation to inactive compounds. Less than 1% of a dose is excreted as 6-MNA. Steady-state plasma concentrations of 6-MNA are not altered in patients with reduced renal function even though the renal excretion of 6-MNA is reduced. This could relate to non-linear protein-binding or increased excretion by other routes. Thus, the dose of nabumetone does not need to be adjusted in patients with mild–moderate renal impairment.

6-MNA preferentially inhibits COX-2. Nabumetone has a dose-related effect on platelet aggregation, but no effect on bleeding time in clinical studies. In most patients, nabumetone needs to be administered only o.d. In a dose of 1g o.d., nabumetone is as effective as other NSAIDs in rheumatoid and osteo-arthritis, and after acute soft tissue injury; RCTs include comparisons with diclofenac, ibuprofen, indometacin, naproxen, and piroxicam. In patients with osteo-arthritis, nabumetone was significantly less gastrotoxic than diclofenac and piroxicam (incidence of major adverse effects (PUBs) over 6 months = 1.1% vs. 4.3%, and no hospitalizations vs. 1.4%). Nabumetone produced fewer endoscopic ulcers over 12 weeks than ibuprofen, and was comparable to ibuprofen + 800mcg misoprostol daily. It is less gastrotoxic than naproxen (endoscopic monitoring for 5 years).

Meta-analysis of 13 studies, incorporating some 50 000 patients, showed that PUBs were at least 10 times less likely than with the comparator NSAIDs. Hospitalization for NSAID-related events was also less frequent (odds ratio 3.7, 95% CI 1.3–10.7). Over some 30 years on the ARAMIS database, nabumetone has had the least hospitalizations for PUBs of all the NSAIDs. In a population-based cohort following up 18 500 patients on NSAIDs for 6 months, diclofenac + misoprostol (as Arthrotec®) and nabumetone resulted in significantly less hospitalizations than naproxen, or diclofenac + misoprostol (given separately); there was one bleed in the nabumetone group vs. 10 with Arthrotec® (although this was not significant at the 5% probability level). The same sample of patients showed significantly fewer deaths from all causes in the nabumetone group compared with Arthrotec®, diclofenac + misoprostol separately, or naproxen, despite comparable patient characteristics.

The decreased propensity for causing gastroduodenal toxicity is related to the fact that nabumetone is:

• non-acidic
• has only a weak uncoupling effect on oxidative phosphorylation, and thus causes only low level disruption (and inactivation) of phospholipids in the gastric protective mucus and mucous membranes.

• undergoes no enterohepatic recirculation of its active metabolite.

In patients with treated hypertension, compared with ibuprofen, fewer on nabumetone had a significant increase in blood pressure (17% vs. 6%). There are no comparative data available for cardiovascular and cerebrovascular morbidity. However, the number of serious adverse events reported for nabumetone (0.5%), and the number of withdrawals from RCTs (<4%), are no greater than with placebo. Bio-availability of 6-MNA 38% (increased by administration with milk). Onset of action 1–2h. Time to peak plasma concentration for 6-MNA 3–6h. Plasma halflife of 6-MNA about 1 day. Duration of action ≥24h.

Cautions
Severe renal impairment (creatinine clearance <30ml/min), active or previous peptic ulceration (see p.000), history of dyspepsia, irritable bowel syndrome, fluid retention, CHF.

6-MNA is highly protein-bound and may displace other highly bound drugs from plasma proteins, e.g. phenytoin, sulphonylureas. Although nabumetone does not normally alter platelet aggregation or affect the INR in anticoagulated patients, there is an isolated report of haemarthrosis and raised INR in a patient taking warfarin. Thus, if nabumetone is prescribed to a patient already taking warfarin, monitor the INR weekly for 3–4 weeks and adjust the dose of warfarin if necessary.

Undesirable effects
For full list, see manufacturer’s SPC. Also see NSAIDs, p.000. Very common (>10%): dyspepsia, abdominal pain, diarrhoea (dose-dependent). Common (<10% >1%): headache, nausea Uncommon (<1% >0.1%): gastro-intestinal ulcers.

Dose and use
Dose reduction is not necessary in patients with mild–moderate renal impairment, but is advisable in severe renal impairment (creatinine clearance <30ml/min). Typically:
• start with 1g o.d. (each evening)
• if necessary, increase to 500mg o.m. and 1g each evening
• if necessary, increase further to 1g b.d.
• in very elderly (80+ years) frail patients, start with 500mg, and limit to 1g daily.

Supply
Nabumetone (non-proprietary) Tablets 500mg, 28 days @ 1g o.d. = £14.

Relifex® (Meda) Tablets 500mg, 28 days @ 1g o.d. = £6.
Oral suspension (sugar-free) 500mg/5ml, vanilla with buttermint flavour, 28 days @ 1g o.d. = £22.