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.[1] 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.[1] 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.[2] 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.[1] 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.[1] Nabumetone has a dose-related effect on platelet aggregation, but no effect on bleeding time in clinical studies.[1,3-5] 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**.[6-8] 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%).[9] Nabumetone produced fewer endoscopic ulcers over 12 weeks than **ibuprofen**, and was comparable to **ibuprofen** + 800mcg **misoprostol** daily[10]. It is less gastrotoxic than **naproxen** (endosopic monitoring for 5 years).[11]

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).[12] Over some 30 years on the ARAMIS database (http://aramis.stanford.edu/), 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).[13] 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.[14]

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%).[15] 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.[1]
Bio-availability of 6-MNA 38% (increased by administration with milk).[1,16]
Onset of action 1–2h.
Time to peak plasma concentration for 6-MNA 3–6h.[2]
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**.[17] 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.[18]

Undesirable effects
For full list, see manufacturer's SPC.
Also see NSAIDs, p.000.
Very common (>10%): dyspepsia, abdominal pain, diarrhoea (dose-dependent)[19]
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,[1] 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.

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