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Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

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Proton pump inhibitors

In 1988, omeprazole became the first proton-pump inhibitor (PPI) to be marketed in the UK. Since then, PPIs have become the mainstay of medical treatment of acid-related gastrointestinal (GI) conditions.

The effectiveness and relative safety of this group of medicines, together with a reduction in their cost as more generic agents have become available, and their availability over-the-counter (OTC) have, perhaps, led to their more liberal use in patients in whom they were never, or are no longer, indicated. PPI use is continuing to rise across Wales.[1]

Although PPIs are generally well-tolerated, with a low incidence of short-term adverse effects, more evidence is coming to light regarding the adverse effects associated with long-term use.

This bulletin discusses the prudent use of PPIs, concerns over long-term use, and considerations for prescribing or reviewing PPI therapy.

Summary

- Proton pump inhibitors are effective treatments for acid-related gastrointestinal conditions, and are generally well-tolerated with a low incidence of short-term adverse effects.
- There is increasing evidence regarding the long-term safety of PPIs; their use has been associated with increased risk of *Clostridium difficile* infection, pneumonia, fracture, hypomagnesaemia, vitamin B_{12} deficiency, and cardiovascular events.
- PPIs should only be initiated if clearly indicated, and for the shortest possible time.
- Advice on lifestyle changes should be offered before prescribing a PPI, particularly to those patients with mild or vague symptoms; patients may be more willing to try self-care if aware of the potential long-term effects of PPIs.
- PPI therapy should be reviewed at least annually and patients encouraged to reduce or stop these medicines where appropriate.
- A step-down approach can be tried for patients in whom symptoms are thought likely to persist below a certain level of acid suppression.

Prescribing PPIs

The effectiveness and general tolerability of PPIs for acid-related GI conditions is not in doubt. However, the evolving evidence regarding potential long-term adverse effects of this group of medicines is concerning. When these potential adverse effects are taken into consideration, the possible risks of treatment may outweigh the potential benefits, particularly in patients without a clear indication for PPIs, or when the patient is at increased risk of medicine-related adverse effects, e.g. frail, older people, or those with significant co-morbidities.

The use of PPIs for mild or vague symptoms, and any 'diagnostic' use **must** be short-term, especially in view of the potential for these agents to produce the type of disease they are designed to treat (see discussion of rebound acid hypersecretion on page 4). There is a risk that patients with no justifiable prior need may end up on continued treatment. Indeed, the NICE recommendations for using PPIs as maintenance, longer-term, are relatively selective and include severe oesophageal stricture, Barrett's oesophagus, and those requiring gastroprotection when considered at high-risk of GI complications with regular NSAID use.[2]

Before prescribing a PPI, the clinician should offer lifestyle advice (Fig.1).[2] In a co-productive relationship (an important part of Prudent Healthcare), patients can benefit from expert lifestyle advice on improving symptoms without the need for a prescription. Patients may be more willing to try self-care to improve their symptoms if they are aware of the potential long-term effects of PPIs.[3]

A medication review should be carried out to identify and stop, where appropriate, medicines known to cause or increase risk of GI bleeding or ulceration, or exacerbate symptoms of dyspepsia (Fig.2).

Fig.1. Lifestyle advice for patients with dyspepsia[3]

Advise people with dyspepsia that symptoms may be improved if they:
• Lose weight (if the patient is overweight) • Reduce fatty food intake • Stop smoking • Stop or reduce alcohol consumption • Stop or reduce the intake of any food or drink associated with worsening symptoms (commonly fatty foods, coffee, chocolate) • Eat meals at regular times, avoiding large or late meals • Avoid bending over or lying down immediately after eating; avoid tight belts or clothing • Use antacid and/or alginate when necessary for immediate symptom relief after meals and at bedtime
Advise people with reflux symptoms on lying down to:
• Avoid meals within 3-4 hours of going to bed • Raise the height of the head of the bed by a few inches (use of more pillows is ineffective) • Use antacid when necessary and/or alginate for immediate symptom relief at bedtime. For patients already receiving a PPI, advise taking the dose in the evening

It is important to avoid a 'prescribing cascade' whereby a PPI may be prescribed, for example, for intolerable dyspepsia exacerbated by treatment with a calcium-channel blocker, when an alternative antihypertensive may be more appropriate.

Where a PPI is considered appropriate and necessary, short-term treatments (usually 4-8 weeks, but see NICE Guideline CG184[2]) should be prescribed initially, with a review on completion of the course. It should be noted that a two-week washout period after PPI use should be allowed before testing for *Helicobacter pylori* with a stool antigen or breath test.[2]

Fig.2. Medicines known to cause, or increase risk of GI bleeding, dyspepsia, or ulceration.[4]

- antiplatelets
- anticoagulants
- corticosteroids
- NSAIDs
- antibiotics
- SSRIs
- bisphosphonates
- calcium-channel blockers
- iron
- nitrates
- nicorandil
- theophylline and aminophylline
- Others: colchicine, levodopa, digoxin, potassium chloride

When prescribing a PPI, it is helpful to discuss with the patient the expected initial duration of therapy and plans for potentially stepping down or stopping treatment thereafter.

Long-term effects of PPIs

The risks associated with continued PPI therapy are not yet fully understood.[5] However, as PPI use has become more widespread (including prescribed and OTC use), evidence is building regarding adverse effects associated with their longer-term use.

Much evidence for the potential long-term effects of PPIs comes from non-randomised observational studies, such as case-control and cohort studies. Although evidence from such studies may be dismissed by some simply because the study was not randomised, it should be noted that randomised controlled trials (RCTs) are often not useful for detecting adverse effects or harms. RCTs have relatively small sample sizes (rare harms will not be detected), restrictive inclusion criteria (not representative of a 'real world' population), and short follow-up (long-term effects are missed). Further, it would be unethical to randomise patients to interventions likely to result in harm without benefit. Despite their inherent biases and confounding, it has been shown that it is more common for observational studies to underestimate rather than overestimate the absolute risk of harm.[6] Evidence of possible harmful effects from well-designed observational studies should therefore not be dismissed.

The potential consequences of long-term treatment with PPIs include increased risks of enteric infections such as *Clostridium difficile* (*C.difficile*), pneumonia, fractures, hypomagnesaemia, vitamin B_{12} deficiency, and a possible interaction with clopidogrel. These potential adverse effects are discussed in turn below. Because much of these data are from observational studies, it is not always possible (or statistically correct) to calculate numbers needed to harm (NNHs).

Enteric infections

As gastric acid is thought to play a principal role in sterilising contents entering the digestive tract, it is biologically plausible that raising the pH of the stomach with acid-suppressive medicines may result in an increased load of pathogenic microbes.

Although a causal link has not yet been proven, the weight of evidence appears to support an association between PPI use and an increased risk of *C.difficile* infection (CDI). Two large meta-analyses suggest an approximately 70% increase in the incidence of *C.difficile*-associated diarrhoea among PPI users compared to non-users.[7,8] A cohort study reported correlation between the degree of acid suppression and the risk of CDI, a potential dose-response relationship.[9]

A further retrospective cohort study of almost 1,200 patients with antibiotic-treated CDI suggested that concurrent use of PPIs increased the risk of recurrence of the infection by 42%.[10] Given the extent of PPI use, the number of potentially avoidable cases of CDI could be significant.

A positive association has also been found between use of PPIs and infection with *Salmonella* spp and *Campylobacter jejuni*, though evidence is limited.[11]

It remains possible that these associations are confounded by other CDI risk factors. However, as acid suppressing medicines, especially PPIs, may be over-prescribed and frequently not reviewed, consideration should be given to stopping or reviewing the need for PPIs in patients with, or at high risk of, CDI.[12] Risk factors for CDI include advanced age, antibiotic treatment (particularly with multiple antibiotics, for long durations, or multiple courses), serious co-morbidities, hospitalisation, and history of CDI (risk of recurrence is 20% for the first episode and 45-60% after the second episode in hospitalised patients).[13]

Pneumonia

Gastric acid suppression can lead to increased bacterial colonisation in the upper GI tract and aspiration of the gut flora during physiological reflux.[14] It has been suggested that there is an association between PPI use and an increased risk of community-acquired pneumonia (CAP).

Several large observational studies and meta-analyses have found this association, particularly within the first seven days of PPI use, with one study estimating a two-fold increase in the risk of CAP associated with PPI use compared with non-use.[15]

A more recent cohort study examined the risk of hospitalisation for CAP with PPIs prescribed as prophylaxis in a cohort of new users of NSAIDs, with the aim of minimising bias from unmeasured confounders such as gastro-oesophageal reflux disease (GORD), which itself may be an independent risk factor for pneumonia. The authors found that, among new users of NSAIDs, PPIs were not associated with an increased risk of hospitalisation due to CAP.[14]

Clearly further research is necessary and the impact on clinical practice is not known. It may be prudent to exercise caution when prescribing PPIs for elderly patients at increased risk of infection and for whom pneumonia may be an important cause of morbidity and mortality, or in those with asthma or chronic obstructive pulmonary disease.[16]

Fractures

In 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety warning about the increased risk of fracture associated with long-term use of PPIs.[17]

Observational studies suggest there may be a modest increase in the risk of hip, wrist, or spine fracture, especially if PPIs are used in high doses over durations of more than one year. This increased risk was observed mainly in elderly patients and it is possible that other risk factors contributed, particularly given the fact the data are inconsistent, with some observational studies not supporting the association.[17,18]

The results from two meta-analyses of observational studies suggest that PPI use increases the risk of fracture by 10-40% above baseline.[17] The possible mechanism for this potential increase in fracture risk remains largely unexplained; proposed theories include decreased absorption of calcium due to increased pH in the small intestine and impaired activity of osteoclasts, thereby altering the bone remodelling process.[19]

Although a causal relationship has not been established, it would be prudent to consider the contribution of PPIs to cumulative fracture risk. In addition, the MHRA advise that patients at risk of osteoporosis who require treatment with PPIs should receive an adequate intake of vitamin D and calcium.[17]

Hypomagnesaemia

It has been postulated that PPIs may inhibit intestinal magnesium absorption via transient receptor potential melastin (TRPM) cation channels.[20]

In 2012, the MHRA issued safety advice following case reports of hypomagnesaemia associated with long-term use of PPIs. The exact incidence is unknown, but severe hypomagnesaemia has been reported infrequently. Most reported cases occurred after one year of treatment, but some occurred sooner. Serious symptoms of hypomagnesaemia (such as fatigue, delirium, convulsions, tetany, and ventricular arrhythmias) can begin insidiously and may be overlooked. In most cases, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.[21]

For patients expected to be on prolonged treatment with PPIs, especially those also taking digoxin or medicines that may cause hypomagnesaemia, such as diuretics, clinicians should consider measuring magnesium levels before starting PPIs and repeat measurements periodically during treatment.[21]

Vitamin B_{12} deficiency

Gastric acid is required to cleave vitamin B_{12} from ingested dietary proteins for essential vitamins to be absorbed. Therefore, PPIs and H_2-receptor antagonists, which suppress the production of gastric acid may, in theory, lead to malabsorption of vitamin B_{12}.[22]

A large US case-control study of more than 200,000 patients found a significantly increased likelihood of vitamin B_{12} deficiency associated with use of PPIs

(65% increased risk) or H_2-receptor antagonists (25% increased risk) for two or more years, compared with no use of either type of medicine.[22]

The study authors conclude that while residual confounding cannot be excluded, the use of these medicines identifies a population at higher risk of vitamin B_{12} deficiency.[22] Further studies will be needed before the clinical significance of this association is clear.

Cardiovascular events

There has been much debate as to whether PPIs reduce the antiplatelet effect of clopidogrel. Pharmacokinetic and pharmacodynamic data suggest that PPIs (to varying degrees) competitively inhibit the CYP2C19 isoenzyme, which metabolises clopidogrel to its active form, thus reducing the ability of clopidogrel to inhibit platelet aggregation. However, the clinical significance of this interaction is not fully understood and the evidence from several observational studies looking at clinical outcomes with this interaction is somewhat conflicting.[23]

In 2010, the MHRA issued safety advice that concomitant use of clopidogrel and either omeprazole or esomeprazole should be avoided unless considered essential, and that the potential risk of a slight reduction in the efficacy of clopidogrel should be weighed against the potential GI benefits of other PPIs. New evidence had become available, which cast some doubt on the clinical relevance of possible interactions between clopidogrel and PPIs, although evidence of a possible interaction with omeprazole and esomeprazole was still a concern.[24]

Some studies have shown an association between PPI use and adverse cardiovascular outcomes (such as rehospitalisation because of myocardial infarction or stroke) in high-risk cardiovascular populations, independently of clopidogrel use.[25] More recently, researchers used a data-mining approach to assess whether there was any association between the use of PPIs and cardiovascular risk in the general population. They found that, among patients with GORD, taking a PPI was associated with a 16% increased risk of myocardial infarction.[26,27] This association does not in itself provide proof of causation, and further studies are needed.

In the meantime, clinicians should be aware of this evolving evidence and consider reducing doses or stopping treatment with PPIs, if possible, in patients with existing cardiovascular disease, and no strong indication for PPI therapy. [28]

Reviewing PPI therapy

NICE recommends that patients treated with PPIs receive regular reviews and should be encouraged to reduce their use of these medicines where possible (unless there is an underlying condition or co-medication that needs continuing treatment). Despite this guidance, PPI use across Wales is increasing at a rate of 5% per year. In the financial year 2014–2015, over 4 million prescriptions for PPIs were dispensed in Wales, and it has been estimated that approximately 9.8% of the population received a PPI prescription.[1] PPI Defined Daily Doses (DDDs) per 1,000 Prescribing Units (PUs) is a National Prescribing Indicator in Wales for 2015-2016.[1]

At patient review, which should be conducted after the initial 4-8 week course of PPI treatment, and at least annually for patients taking PPIs longer-term, the need for ongoing therapy (particularly at full treatment doses) should be assessed. If symptoms are well controlled by the initial PPI treatment course, and if there is no strong indication for long-term therapy, a step-down in treatment can be considered. It has been estimated that up to 30% of patients may be able to stop a PPI immediately after the initial course of therapy without experiencing symptoms.[29]

Stopping or reducing therapy may not be appropriate for some patients, e.g. those taking PPIs for the prevention of NSAID-associated ulcers, Barrett's oesophagus, or some of those patients with severe oesophagitis complicated by past strictures, ulcers, or haemorrhage.[30]

Inappropriate continuation of prophylactic PPIs can occur following hospital discharge. Ideally, risk should be reassessed during the course of a hospital stay, and if it is necessary to issue a supply at discharge, the intended duration of treatment should be specified.[30]

Stepping down PPI therapy

The main problems associated with stopping or reducing treatment with PPIs are the risk of **relapse or recurrence** of the condition being treated, an increased risk of **bleeding** (depending on the indication), and possible **rebound acid hypersecretion.**

Rebound acid hypersecretion is an increase in gastric acid secretion above pre-treatment levels, and may occur after stopping PPI therapy. Two systematic reviews found no strong evidence for rebound acid hypersecretion but the authors acknowledged heterogeneity between the included studies and methodological weaknesses.[29,31,32] Studies in healthy volunteers have shown reflux-like symptoms within two weeks, and for at least four weeks after withdrawal from PPI therapy.[30] This rebound hypersecretion could present as a worsening of symptoms that could be mistaken for disease relapse.

Warning patients about rebound acid hypersecretion and reassuring them about how to manage this with simple antacids might reduce the risk of re-initiation of the PPI.[5]

A step-down approach, rather than abrupt cessation, may be more acceptable in those patients in whom symptoms are thought likely to persist and become troublesome below a certain threshold of acid suppression, or in whom the possibility of rebound acid hypersecretion is a concern (see Fig.3).[30]

If a step down does not adequately control symptoms, resume with the lowest effective dose and frequency of PPI, and consider future step-down where appropriate.

Patients may be reluctant to reduce the dose or frequency of their PPI for fear that their symptoms may return. It can be explained that:

- reduced PPI therapy can maintain symptom relief
- symptom-driven therapy means taking fewer tablets
- there is less risk of adverse effects when fewer medicines are taken.[33]

Fig.3. Approximate dosage equivalences for PPIs.[2]

PPI	Full/standard dose	Low dose (on demand dose)	Double dose
omeprazole	20mg once a day[a]	10mg once a day[a,c]	40mg once a day[a]
lansoprazole	30mg once a day	15mg once a day	30mg twice a day[c]
pantoprazole	40mg once a day	20mg once a day	40mg twice a day[c]
rabeprazole	20mg once a day	10mg once a day	20mg twice a day[c]
esomeprazole	20mg once a day[a]	not available	40mg once a day[a,b]

[a] Higher doses are used for severe oesophagitis (see NICE Guideline CG184). [2]
[b] 40mg is recommended as a double dose of esomeprazole as the 20mg dose is considered equivalent to omeprazole 20mg.
[c] Off-label dose for GORD.

PPIs and NSAIDs

Not all patients prescribed an NSAID will require gastroprotection to prevent GI adverse effects. Before deciding whether gastroprotection is required, consider prescribing an alternative to an NSAID. When an NSAID is required, it should be prescribed at the lowest effective dose for the shortest period of time.

If a person is at high risk of GI adverse effects and requires ongoing therapy with an NSAID, a PPI (at a dose licensed for gastroprotection) can be considered for prevention of chronic NSAID-related endoscopic gastric and duodenal ulcers. An H_2-receptor antagonist such as ranitidine given at twice the usual dose (unlicensed) or misoprostol are effective alternatives.[34,35]

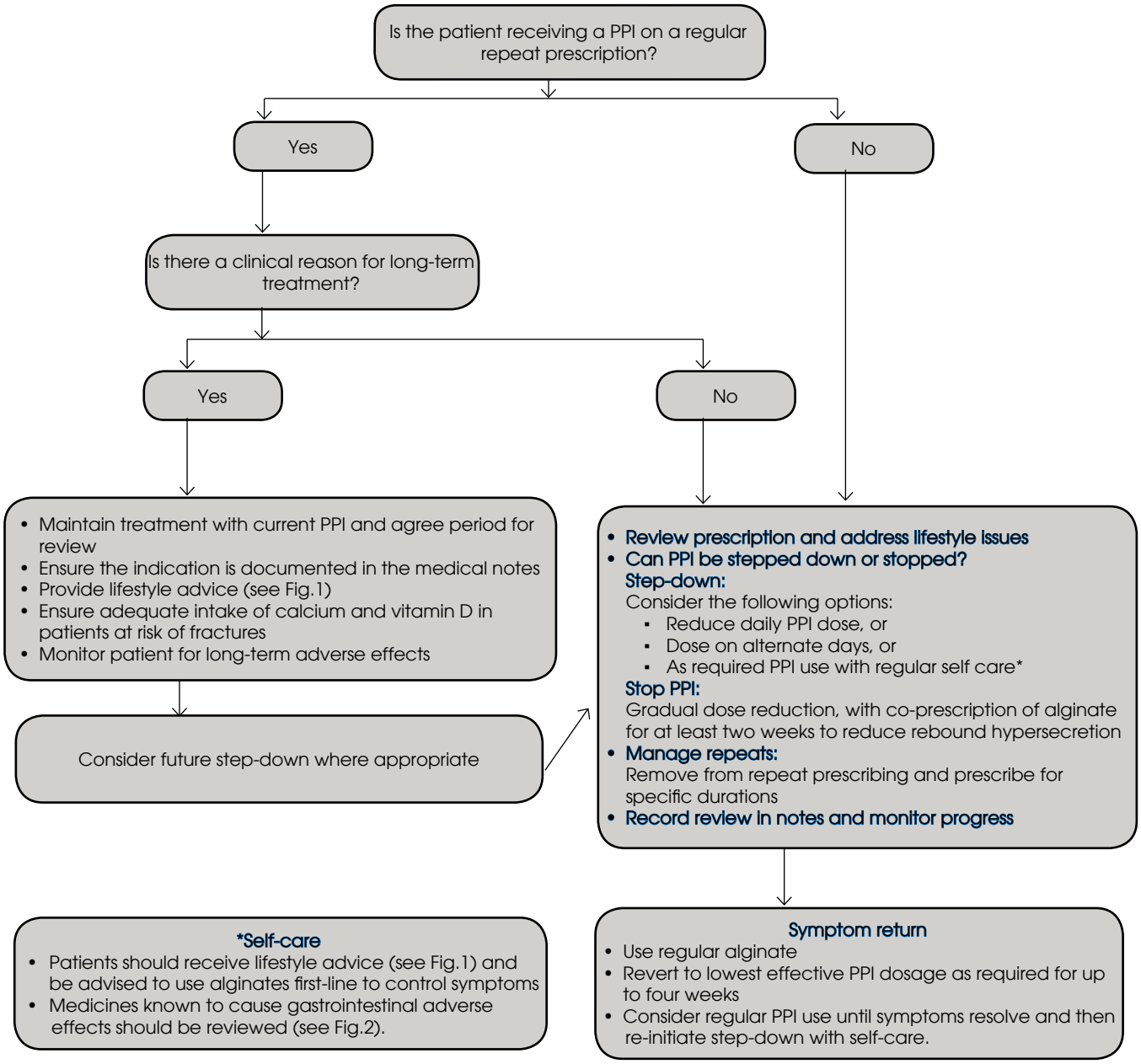
People are at high risk of serious NSAID-induced GI adverse events if they have one or more of the following risk factors:[36]

- Using the maximum recommended dose of an NSAID
- Age ≥ 65 years
- History of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation
- Concomitant use of medicines known to increase the likelihood of upper GI adverse events, e.g. anticoagulants, aspirin (even low dose), corticosteroids, and antidepressants (SSRIs, venlafaxine, duloxetine)
- Serious co-morbidity, such as cardiovascular disease, hepatic or renal impairment (including dehydration), diabetes, or hypertension
- Requirement for prolonged NSAID use including people with:
  - Osteoarthritis or rheumatoid arthritis of any age
  - Chronic low back pain and age ≥ 45 years

Additional risk factors to consider include:

- The type of NSAID used
  - Lowest risk: ibuprofen (but serious and fatal GI adverse effects have still been reported)
  - Intermediate risk: diclofenac, naproxen, ketoprofen, piroxicam, and indometacin
  - Highest risk: azapropazone (no longer available in the UK)
- The presence of *Helicobacter pylori* infection
- Excessive alcohol use
- Heavy smoking

Fig.4. Reviewing PPI therapy.[5]



Conclusion

Although the absolute risk of the adverse outcomes associated with PPI use discussed earlier is low, the best way to reduce the risk is to ensure that they are only initiated where clearly indicated, with careful consideration, and that they are used for the shortest time that is appropriate.[30] By stopping or reducing treatment when appropriate, the benefits can be preserved whilst the risk of serious adverse effects will be reduced.[33]

Summaries of Product Characteristics (SPCs) should be consulted for full prescribing information.
References available at www.wemerec.org

Welsh Medicines Resource Centre
All Wales Therapeutics & Toxicology Centre
Academic Building, University Hospital Llandough, Penarth,
Vale of Glamorgan CF64 2XX

Tel: 029 2071 6117 Email: wemerec@wales.nhs.uk

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