PostScRxipt - ExtRa

NHS Greater Glasgow

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STANDARD vs. MODIFIED RELEASE ISOSORBIDE MONONITRATE

- **Isosorbide mononitrate is widely used for the prophylactic treatment of angina pectoris.**
- **There is no evidence that once-daily modified-release preparations are more effective than standard-release preparations given by asymmetric twice-daily dosing.**
- **There is no evidence that a once-daily preparation significantly improves compliance compared with a twice-daily regimen.**
- **The additional costs incurred by the routine use of once-daily modified-release preparations of isosorbide mononitrate cannot be justified.**
- **Therefore, standard-release isosorbide mononitrate is the formulation of choice in NHS Greater Glasgow.**
- **Switching to twice-daily regimens in half of the patients on once-daily preparations, where appropriate, could save more than £100,000 per annum.**

Introduction

What is it?

Isosorbide mononitrate (ISMN) is widely used for the prophylaxis of angina pectoris. As the active metabolite of isosorbide dinitrate, ISMN does not require first-pass metabolism for activation and its longer half-life allows for twice-daily dosing.

At present there are twelve once-daily modified-release (m/r) formulations of ISMN available (e.g., Imdur®, AstraZeneca and Elantan®, Schwarz). These are claimed to have benefits over standard-release preparations with regard to the development of nitrate tolerance and improved patient compliance.

How much is prescribed?

There were 39,076 prescriptions for ISMN m/r (mainly Imdur®) in NHS Greater Glasgow (NHSGG) primary care division in 2004/05, at a total cost of nearly £600,000 (in secondary care approximately 60,000 doses were issued). If half of this prescribing were replaced with ISMN standard-release tablets, annual savings of around £105,000 - £190,000 across NHSGG could be made (depending on the brand of ISMN m/r that was prescribed).

Evidence

How does efficacy between standard and once-daily ISMN compare?

There are no large-scale randomised double-blind controlled clinical studies which compare the efficacy of once-daily ISMN m/r with standard-release ISMN given by asymmetric twice-daily dosing for the prophylactic treatment of angina.

What about tolerance?

Some degree of nitrate tolerance is observed after chronic dosing with any nitrate preparation.[1,2] The most important issue when prescribing nitrates is to use a dosing strategy which protects against ischaemia while avoiding the development of tolerance. This can be achieved with either standard-release ISMN tablets given by asymmetric twice-daily dosing (e.g. 08.00h and 14.00h)[3,4] or by the use of once-daily ISMN m/r preparations.[5]

What about compliance?

Modified-release preparations are claimed to lead to improved patient compliance; however, there is little good quality evidence suggesting worthwhile or significant differences between once-daily and twice-daily regimens.[6,7] In addition, taking a once-daily regimen incorrectly can lead to similar problems to those encountered when a conventional formulation is taken inappropriately, such as tolerance (by taking the dose more than once a day), or underprotection (if the dose is missed).

Safety

Will patients come to harm if switched?

Most nitrate-induced adverse effects are dose-related. Headache is the most common, the incidence is similar for equivalent doses of both standard and m/r preparations.[8] Other adverse effects include postural hypotension, flushing, and dizziness. The severity and incidence of these effects decrease with continued use.

Therapeutic equivalent doses for switching patients from m/r preparations to asymmetric doses are given below.

Dose of m/r preparation	Asymmetric dose
25 mg once daily	10 mg twice daily
30 mg once daily	10 mg twice daily
40 mg once daily	20 mg twice daily
50 mg once daily	20 mg twice daily
60 mg once daily	20 mg twice daily
100 mg once daily	40 mg twice daily
120 mg once daily	40 mg twice daily

Patients within NHSGG primary care division have been switched from once-daily m/r preparations to asymmetric twice-daily preparations by practice pharmacists successfully without loss of symptom control or increased incidence of adverse effect; however, it would be prudent to monitor such patients initially.

Place in Therapy

What other options are there?

Patients who require regular angina prophylaxis should be treated with a beta-blocker, low-dose aspirin, as required sublingual GTN and a statin if appropriate.[9] Patients who have contraindications to, or are intolerant of, beta-blockers should receive verapamil or diltiazem. Where neither is appropriate another calcium-channel blocker, an oral nitrate or a potassium channel opening agent are suitable alternatives.

When should the standard release or modified release preparations be used?

Where ISMN therapy is indicated, standard-release tablets given by asymmetric twice-daily dosing is the formulation of choice within NHS Greater Glasgow. Single doses above 40 mg daily have not been shown to confer additional benefit.[8]

In the absence of supportive evidence indicating improved clinical outcome with once-daily ISMN m/r preparations, the increased cost associated with their routine use cannot be justified. They should be reserved only for those patients with proven difficulties in taking asymmetric twice-daily ISMN, such as elderly patients with cognitive impairment in whom all other medicines are once-daily.

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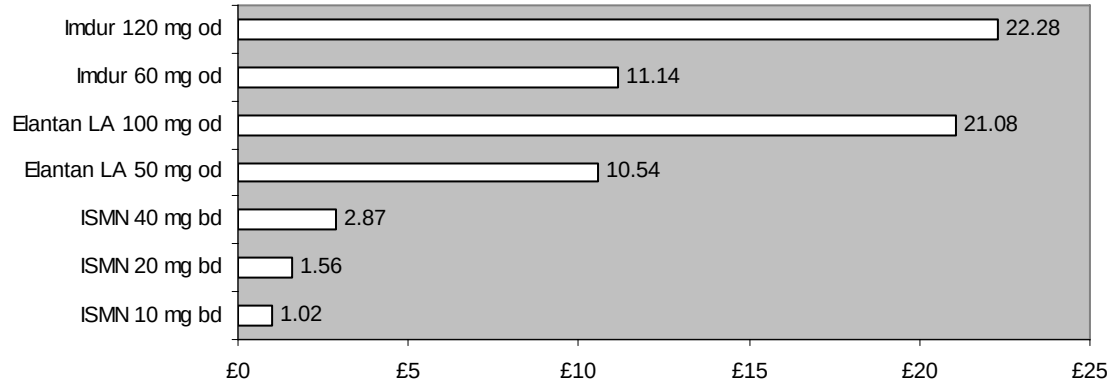
How much do they cost?

Cost for 28 days treatment (prices from Scottish Drug Tariff/MIMS November 2005)



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