

# **DISCUSSION PAPER- REVIEW OF STANDARD RELEASE VS MODIFIED RELEASE ORAL NITRATES FOR PREVENTION OF ANGINA**

**Report to Area Prescribing Committee April 2010**

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## **Introduction**

Angina is used to describe a clinical syndrome of chest pain or pressure precipitated by activities such as exercise or emotional stress which increase myocardial oxygen demand. Nitrates act directly on the vascular smooth muscle to produce venous and arterial dilatation, reducing pre-load, after-load and oxygen demand.<sup>1</sup> Short-acting, sublingual glyceryl trinitrate should be used for immediate relief of an episode of angina, or before activities that are likely to precipitate angina. Long-acting oral nitrates are used regularly to decrease the frequency and severity of anginal symptoms. Isosorbide mononitrate (ISMN) is generally preferred to isosorbide dinitrate (ISDN) due to the fact ISMN, as the active metabolite of isosorbide dinitrate, does not require first-pass metabolism for activation and its longer half-life allows for twice-daily dosing.<sup>2,3</sup>

## **Scope**

The aim of this paper is to review the evidence relating to advantages/ disadvantages of the standard release and modified release oral nitrate preparations, and to present recommendations for consideration by the appropriate committees in relation to these preparations. It is not the aim of this paper to produce guidelines/ recommendations for the overall treatment/ prevention of angina.

As the vast majority of oral prophylactic nitrates prescribed are preparations of ISMN, this paper will consider these only. There is only one modified release preparation of ISDN (Isoket Retard).

## **Isosorbide Mononitrate (ISMN) Prescribing in Surrey NHS region**

ISMN was introduced into the UK in 1983 and is the active metabolite of ISDN. At present, there are 18 once daily modified release formulations (m/r) of ISMN available.<sup>4</sup>

A review of prescribing data<sup>5</sup> over the last 6 months has revealed a total of £195,758 spent on 28,901 ISMN items. Only £17,094 of this equates to standard release ISMN preparations- however this relates to 12,789 items- an average cost of £1.34 per item. This leaves £178,664 spent on 16,104 ISMN m/r items- an average cost of £11.09 per m/r item. If only half of these ISMN m/r preps were switched to standard release preparations, calculating cost savings from the average cost per item could see annual savings of around £150,000. If 75% of ISMN m/r preparations were switched to standard release preparations, this could release annual cost savings of around £235,520. This is an average figure and actual savings will vary depending on which brands of ISMN m/r were replaced.

## **Review of evidence for ISMN m/r preparations versus ISMN standard release preparations**

### **Efficacy**

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.<sup>3</sup>

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Niemeyer et al <sup>12</sup> report the results of a self-controlled 6-month study looking at the effects on symptoms and quality of life of multiple-dose and once-daily nitrate therapy in 1212 patients with stable angina pectoris. The effects of the two treatment regimens on pain index and number of additional sublingual nitrate tablets required were not different. However, they concluded that patients taking the once daily preparation reported a better quality of life as estimated by improvement of mobility and distress indices.

### **Nitrate tolerance and Compliance**

The benefits of m/r preparations over standard release preparations are claimed to be in reduced nitrate tolerance and increased patient compliance. There is substantial evidence that nitrate tolerance can be prevented by an adequate nitrate-free or nitrate-low period during each 24 h dosing interval. However, a nitrate-free interval carries the risk of a rebound increase in myocardial ischaemia. Myocardial ischaemia has a marked circadian rhythm. All ischaemic events (total ischaemic burden, myocardial infarction and sudden cardiac death) are most frequent in the hours immediately after waking. Oral anti-ischaemic prophylaxis should ideally provide protection during this critical period, in order to minimize symptoms, maximize exercise capacity and perhaps also to reduce the risk of clinical events.<sup>6</sup>

Some degree of nitrate tolerance is observed after chronic dosing with any nitrate preparation.<sup>7,8</sup> ISMN in qds, tds and and 12 hourly bd dosing regimens produces tolerance.<sup>13</sup> 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)<sup>9,10</sup> or by the use of once-daily ISMN m/r preparations.<sup>11</sup> However, none of the dosing regimens of any oral, long-acting nitrate (including IS-5-MN) provide 24 hour antianginal and anti- ischemic effects.<sup>13</sup>

Thadani et al <sup>10</sup> report a multicenter, placebo-controlled, parallel-group, double-blind, randomized study in 116 patients with stable exertional angina who stopped treadmill exercise because of angina pectoris. Patients received single-blind placebo for 1 week followed by either 20 mg of ISMN standard release tablets (n = 60 patients) or placebo (n = 62 patients) twice daily at 0800 hours and 1500 hours for 2 weeks. Compared with placebo recipients, patients receiving ISMN standard release tablets walked significantly longer at 2, 5, and 7 hours after the 0800-hour dose (P < 0.01) and at 2 and 5 hours after the 1500-hour dose (P < 0.01). Before the morning (0800-hour) dose, exercise duration increased by 0.53 minutes in placebo recipients and by 0.85 minutes in those receiving IS-5-MN therapy (P = 0.10). Neither nocturnal nor early-morning anginal attacks increased during IS-5-MN therapy compared with placebo. Headaches occurred in 19 (32%) patients in the IS-5-MN group and in 9 (15%) patients in the placebo group but necessitated discontinuation of treatment in only 2 (3%) patients in the IS-5-MN group. They concluded that ISMN 20 mg twice daily given 7 hours apart, was well tolerated and improved exercise performance for 7 hours after the morning dose and for 5 hours after the afternoon dose without evidence of development of pharmacologic tolerance. No rebound increase in anginal attacks was found.

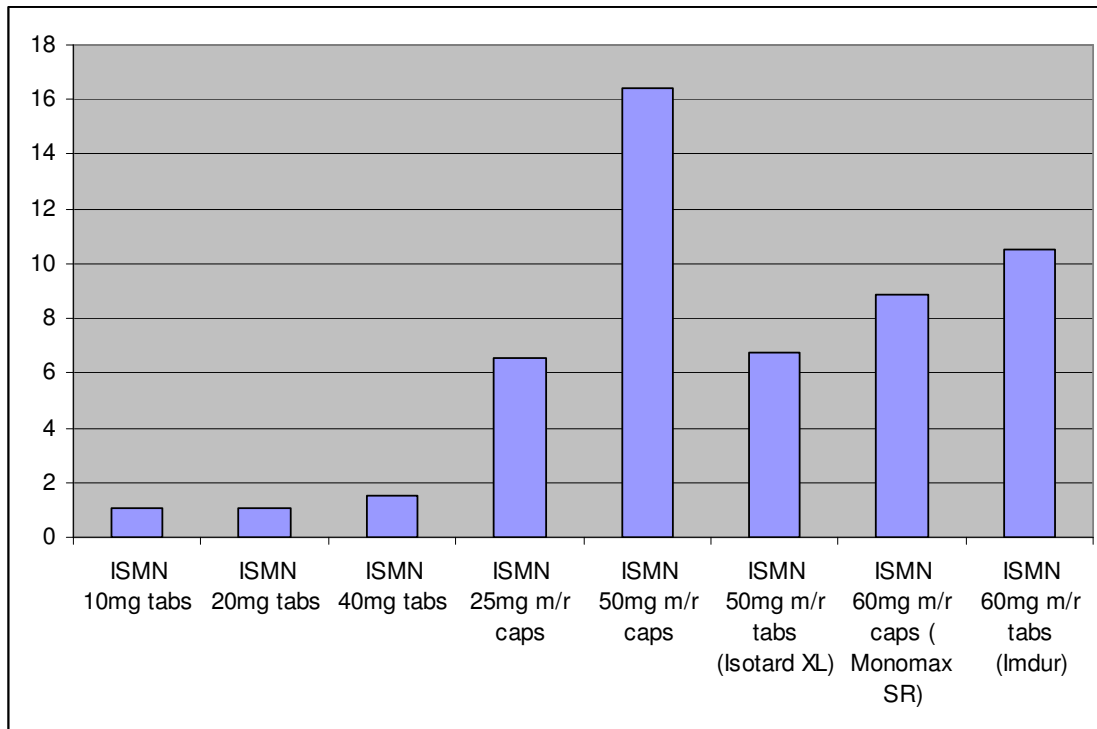
Comparing compliance between the asymmetric bd dosing of standard release ISMN tablets and the once daily ISMN s/r preparations, large studies have shown no significant differences between once-daily and twice-daily regimens.<sup>3</sup>

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 <sup>14</sup> (by taking the dose more than once a day), or underprotection (if the dose is missed).<sup>3</sup> Norlander et al <sup>14</sup> report the results of a randomized, double-blind cross-over study in 37 patients to assess the efficacy of once- and twice-daily dosage regimens of 60 mg isosorbide-5-mononitrate, in a controlled-release formulation (5-ISMN Durules, Astra). Anginal attack rate and nitroglycerin consumption was significantly lower during the once-daily dosage period as compared with placebo; this difference was not evident during the twice-daily administration of the drug. Controlled-release 5-ISMN 60 mg given once daily was effective in angina pectoris patients for at least 9 h after the dose and showed no clinical signs of tolerance after 2 weeks of the treatment. Attenuation of the clinical effect was observed with the twice-daily (in 12 h intervals) dosage regimen, presumably caused by constantly high 5-ISMN plasma concentration.

## **Cost**

The graph below shows the cost of 28 days treatment with various ISMN preparations.

Prices are from Drug Tariff March 2010.



## **Safety**

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. Other adverse effects include postural hypotension, flushing, and dizziness. The severity and incidence of these effects decrease with continued use.<sup>14</sup>

## **Precedence**

A number of other regional areas have implemented 'switch' policies.

Patients within NHS Greater Glasgow primary care division have been switched from once-daily m/r preparations to therapeutically equivalent asymmetric twice-daily preparations by practice pharmacists successfully without loss of symptom control or increased incidence of adverse effect; however, they advise it would be prudent to monitor such patients initially.<sup>14</sup> Where ISMN therapy is indicated, standard-release tablets given by asymmetric twice-daily dosing is the formulation of choice within NHS Greater Glasgow. ISMN m/r preparations are 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.

Gwent Healthcare NHS Trust, in agreement with the five local health boards in Gwent, has supported a switch policy from ISMN m/r preparations to ISMN standard release. The purpose of the switch is to benefit the local health economy by using cost effective and equally efficacious medicines. Gwent Healthcare NHS Trust will undertake to initiate all new patients with standard release isosorbide mononitrate, as a twice daily regime, when a nitrate is considered appropriate treatment, in line with suitability of the patient for the switch- such as a patient's ability to comprehend or comply with doses at 8am and 2pm (times usually suggested), the quantity of other medication a patient is on, as those taking a

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substantial number of medicines or on complex regimen may benefit from a single daily dose in terms of concordance, the timing of anginal attacks, as for those patients with nocturnal angina a twice-daily dose would be inappropriate, doses of isosorbide mononitrate M/R above 60mg daily where no equivalence is stated.<sup>15</sup>

A publication to general practitioners and pharmacists, produced by Oxfordshire Health Authority Prescribing Team in 1996, recommends a switch from ISMN m/r 60mg od to ISMN standard release tablets 20mg 8am, 20mg 2pm or 20mg 8am, 20mg 6pm.<sup>16</sup>

Weatherhead et al<sup>17</sup> report a small study from Hartlepool which investigated the possibility of successfully transferring patients from m/r to plain nitrates. The authors concluded that, if managed carefully, therapeutic substitution of m/r oral nitrates can be achieved without apparent risk of loss of symptom control or increased incidence of adverse effects.

### **Recommendation**

Taking the above information into account, the committees are asked to consider supporting a policy to:

1. Review patients for switching from ISMN m/r preparations to standard release ISMN preparations, in line with the considerations below.
2. Also undertake to initiate all new patients with standard release ISMN tablets, as a twice daily regime, when a nitrate is considered appropriate treatment, in line with the considerations below.

The following must be taken into consideration when assessing the suitability of patients for switches<sup>14,15</sup>:

- A. A patient's ability to comprehend or comply with doses at 8am and 2pm (times usually suggested).
- B. The quantity of other medication a patient is on, as those taking a substantial number of medicines or on complex regimen may benefit from a single daily dose in terms of concordance.
- C. The timing of anginal attacks, as for those patients with nocturnal angina a twice-daily dose would be inappropriate.

Therapeutically equivalent doses are shown in the table below:<sup>14,15</sup>

<b>Dose of ISMN m/r preparation</b>	<b>Assymetric dose of standard release ISMN tablets (8am and 2pm)</b>
25mg od	10mg bd
30mg od	10mg bd
40mg od	20mg bd
50mg od	20mg bd
60mg od	20mg bd

There appears to be some discrepancy about switching patients who are taking a dose of ISMN m/r higher than 60mg od. NHS Greater Glasgow<sup>14</sup> suggest a dose equivalence as below:

<b>Dose of ISMN m/r preparation</b>	<b>Assymetric dose of standard release ISMN tablets (8am and 2pm)</b>
100mg od	40mg bd
120mg od	40mg bd

Gwent Healthcare NHS Trust have not made any recommendations for the equivalent dose of ISMN standard release tablets for any dose of ISMN m/r over 60mg od.

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