Q&A 101.5

# How should conversion between doxazosin formulations be carried out in patients with hypertension?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Date prepared: November 2015

## Background

Doxazosin is a long acting alpha-1 adrenergic antagonist which is licensed for the treatment of hypertension. It is available as both immediate and modified release tablets (also referred to as GITS which means doxazosin in a gastrointestinal therapeutic system). The immediate release (standard) preparation is initiated at 1mg once daily, increasing after 1-2 weeks as necessary to 2mg once daily, and thereafter 4mg once daily to a maximum of 16mg daily. The modified release preparation is initiated at a dose of 4mg daily, increasing to 8mg daily after 4 weeks if necessary. There are a number of modified-release doxazosin preparations available, such as Cardura XL, Doxadura XL, Raporsin XL and Slocinx XL.(1) The GITS formulation was developed to enhance the pharmacokinetic profile allowing more uniform plasma levels and eliminating at least two dose titration steps that may be needed with standard doxazosin, whilst reducing the likelihood of significant first dose hypotension.(2)

This difference in dosing has led to confusion on how to convert patients from one formulation to another.

NICE, with the British Hypertension Society, recommends that the current place of alpha-1 adrenergic antagonists such as doxazosin in the treatment of hypertension is as fourth line treatment.(3) Current evidence does not support the use of alpha-1 adrenergic antagonists for initial treatment of hypertension.(3) Therefore a patient prescribed doxazosin is likely to be taking a number of other antihypertensive medications.

## Answer

The pharmacological and pharmacokinetic properties of some of the currently available doxazosin preparations are shown in table 1. The serum half-life of doxazosin is the same for both immediate- and modified-release preparations, allowing for once-daily administration for either formulation. The advantages of the modified-release preparation are more consistent plasma doxazosin levels and no dose titration phase is needed. (4)

The efficacy of doxazosin GITS 4mg or 8mg compared with immediate-release doxazosin were compared in an integrated analysis of two multicentre studies (n=683 in the per protocol analysis). The primary endpoint of both studies, and of the combined analysis, was the proportion of patients in the per protocol analysis with a sitting diastolic blood pressure (BP) ≤90mmHg or a decrease of ≥10mmHg measured 24-hours post dose. Both products produced gradual but sustained reduction in blood pressure, with maximal effects reached after 5 weeks of therapy. The blood pressure response to doxazosin GITS was achieved without the need for a titration period. Blood pressure control as defined above was achieved by similar proportions of patients in each group: 64% taking doxazosin GITS (mean dose 5.4mg) and 68% taking standard doxazosin (mean dose 4.7mg). Of those patients on standard doxazosin tablets who responded to a dose of 4mg or less (64.5% of the group), 56% of them needed a dose of 2mg/day, compared with 64.4% who responded with a doxazosin GITS 4mg/day dose. Overall a similar number of patients in each doxazosin group suffered from adverse events (137, 43.1% in the GITS group and 135, 43.1% in the standard group). Fewer patients with doxazosin GITS discontinued therapy compared with standard therapy because of side-effects (5.3% versus 9.3%).(4)

**Table 1: Pharmacological and pharmacokinetic properties of some of the UK available doxazosin preparations.**

| Product | Bioavailability | Peak blood levels | Max. hypotensive effects | Half-life |
|---|---|---|---|---|
| **Cardura XL (modified release) (5)** | 54% (4mg XL)<br>59% (8mg XL) (relative bioavailability compared to immediate release Cardura) | 8-9 hours post dose. Peak plasma levels are approximately 1/3 of those of the same dose of immediate release doxazosin tablets | Blood pressure reductions present throughout the day | Terminal elimination half-life is 22 hours |
| **Doxdura XL(6)**<br>**Raporsin XL(7)**<br>**Slocinx XL (8)**<br>**Cardozin XL(9)** | 54% (4mg XL)<br>59% (8mg XL) (relative bioavailability compared to the immediate release form) | 6-8 hours post dose. Peak plasma levels are approximately 1/3 of those of the same dose of immediate release doxazosin tablets | Blood pressure reductions present throughout the day | |
| **Cardura (immediate release) (10)** | ~ 2/3 of the dose (10) | 2-3 hours post dose (11) | 2-6 hours post dose (11) | |

## Switching from modified-release to standard preparation

The initial dose of standard doxazosin is 1mg, to minimise the potential for postural hypotension and/or syncope. Dosage should then be increased to 2mg after 1-2 weeks and then 4mg if necessary, up to a maximum of 16mg daily.(1,10,11)

The following needs to be taken into consideration when switching a patient from the modified release (also known as GITS) to the standard preparation:

- If used according to NICE/BHS guidelines, doxazosin therapy is additional to other antihypertensive medications.
- The patient will have been taking at least 4mg of doxazosin MR, as well as a number of other antihypertensive medications. Is it clinically reasonable to start standard doxazosin at a lower dose of 1mg in order to minimise potential postural hypotension and other unwanted effects.

In the absence of any firm recommendations from the manufacturers of modified-release doxazosin, there are two possible strategies to convert patients from modified release to standard doxazosin and both scenarios require follow up monitoring of blood pressure and patient tolerability:

1. Give half the dose of modified-release doxazosin as standard doxazosin, i.e. 4mg XL switched to 2mg standard. There may be some patients who may require a higher dose and subsequent dose titration may be required.

   Or

2. Give the same dose as modified-release doxazosin but there may be some patients who suffer orthostatic hypotension and need a lower dose and subsequent dose titration may be required.

The alternative is to comply with the licensed dosing recommendations and initiate therapy at 1mg daily, increasing at weekly/fortnightly intervals.(10,11)

### Switching from standard preparation to modified-release (GITS)

The initial dose of modified-release doxazosin is 4mg once daily and this will control over 50% of patients with mild to moderate severity hypertension. The optimal effects of doxazosin may take up to 4 weeks to be seen. If necessary, the dosage may be increased following this period to a maximum of 8mg once daily according to patient response. Clinically significant reductions in blood pressure are present throughout the day and at 24 hours post dose.(5-9)

Patients who are switched from standard doxazosin tablets to modified release should start treatment with modified-release doxazosin 4mg/day, which should be titrated upwards to 8mg as necessary.(5-9) This requires follow up monitoring of blood pressure and patient tolerability.

## Summary

The recommendations for patients who are currently taking modified-release doxazosin and are being switched back to standard release formulations of doxazosin are not well-defined.
The dose of standard doxazosin could be re-initiated at 1mg daily, as if newly starting therapy, or at half the modified-release doxazosin dose.
In both instances some patients will need a dose increase, titrated until the desired efficacy is achieved.
Alternatively, the dose of the immediate release doxazosin could be initiated at the same dose as the modified-release doxazosin dose, but then some patients may need a dose reduction.
Either approach requires follow up monitoring of blood pressure and patient tolerability.

If patients are currently taking standard doxazosin and need to be transferred to modified-release doxazosin, the initial dose is 4mg daily which can be increased to 8mg daily as necessary. This requires follow up monitoring of blood pressure and patient tolerability.

### Limitations

- The BNF provides recommendations for switching from the standard doxazosin preparation to the modified release preparations, but not vice versa. (1)
- This Q&A should be used in conjunction with UKMI Q&A 22 “What is the evidence comparing doxazosin XL with standard doxazosin?” which can be found via www.evidence.nhs.uk

### References


(1) Joint Formulary Committee. British National Formulary online edition. London: BMJ Group and Pharmaceutical Press. Acessed via www.medicinescomplete.com on 17/11/2015
(2) Chung M, Vashi V, Puente J et al. Clinical pharmacokinetics of doxazosin in a controlled-release gastrointestinal therapeutic system (GITS) formulation. Br J Clin Pharmacol 1999; 48:678-687.
(3) National Institute for Health and Care Excellence. NICE Clinical Guideline 127: Hypertension in adults: diagnosis and management. August 2011. Accessed via www.nice.org.uk/guidance/CG127 on 17/11/2015
(4) Os I, Stokke HP. Effects of doxazosin in the gastrointestinal therapeutic system formulation versus doxazosin standard and placebo in mild-to-moderate hypertension. J Cardiovasc Pharmacol 1999; 33:791-797.
(5) Summary of Product Characteristics. Cardura XL. Pfizer Limited. Date of revision of the text: 28/07/2015. Accessed via www.emc.medicines.org.uk on 17/11/2015.
(6) Summary of Product Characteristics. Doxadura XL 4mg prolonged release tablets. Discovery Pharmaceuticals. Date of revision of the text: 13/02/2015. Accessed via www.emc.medicines.org.uk on 17/11/2015.
(7) Summary of Product Characteristics. Raporsin XL. Actavis UK Ltd. Date of revision of the text: 22/09/2015. Accessed via www.emc.medicines.org.uk on 17/11/2015
(8) Summary of Product Characteristics. Slocinx XL 4mg Prolonged-release Tablets. Zentiva. Date of revision of the text: 18/06/2015. Accessed via www.emc.medicines.org.uk on 17/11/2015.

(9) Summary of Product Characteristics: Cardozin XL 4mg Prolonged-release Tablets (doxazosin) (Arrow). Actavis UK Ltd. Date of revision of the text: 21/01/2014. Accessed via www.emc.medicines.org.uk on 17/11/2015.
(10) Summary of Product Characteristics: Cardura tablets 2mg. Pfizer Ltd. Date of revision of the text: 28/07/2015. Accessed via www.emc.medicines.org.uk on 17/11/2015.
(11) Summary of Product Charactetristics: Doxazosin 8mg Tablets. Milpharm Ltd. Date of revision of the text: 08/09/2015. Accessed via www.emc.medicines.org.uk on 17/11/2015

## Quality Assurance

### Prepared by
Lekha Shah, London Medicines Information Service, Northwick Park Hospital, Harrow, Middlesex, (based on earlier work by Alexandra Denby, London Medicines Information Service).

### Contact
lnwh-tr.medinfo@nhs.net

### Date Prepared
November 2015

### Checked by
Sheena Vithlani, London Medicines Information Service, Northwick Park Hospital, Harrow, Middlesex.

### Date of check
December 2015

### Search strategy
- Embase: "((DOXAZOSIN )) AND (HYPERTENSION) AND (CONTROLLED-RELEASE FORMULATION))" Date:18/12/2015
- Medline: "(DOXAZOSIN/.) AND (*HYPERTENSION/.) AND (DELAYED-ACTION PREPARATIONS/.)" Date:18/12/2015
- Pubmed: ("Doxazosin"[Mesh] AND "Hypertension"[Mesh]) AND "Delayed-Action Preparations"[Mesh] Date: 04/01/2016
- Internet search using Google for local policies for switching between doxazosin products.