



## Therapy fact sheet

# Nifedipine Gastrointestinal Therapeutic System (Adalat<sup>®</sup> GITS)

### Adalat<sup>®</sup> GITS – best evidence in class

- Adalat<sup>®</sup> (nifedipine) is a well-established calcium channel blocker (CCB) that has been widely used as an antihypertensive and anti-anginal agent for many years.
- The unique GITS formulation consists of a drug reservoir surrounded by a semi-permeable membrane, which has a single precision-laser-drilled pore on the drug-reservoir side.
- The Adalat<sup>®</sup> GITS formulation delivers a constant plasma level of nifedipine over 24 hours, avoiding unwanted side effects that may be seen with shorter-acting agents.
- Adalat<sup>®</sup> GITS is one of the most thoroughly investigated CCBs with the best evidence in its class.
- The clinical efficacy of Adalat<sup>®</sup> GITS, including in patients with increased cardiovascular (CV) risk, has been demonstrated in a number of important clinical trials. A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION)<sup>1</sup> extends the evidence base for Adalat<sup>®</sup> GITS established by the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT)<sup>2</sup> and the Evaluation of Nifedipine and Cerivastatin on Recovery of Coronary Endothelial Function (ENCORE) trials.<sup>3,4</sup>
- In addition to its blood pressure (BP) lowering effect, these studies confirmed that Adalat<sup>®</sup> GITS has vascular-protective properties, which have been related to improved clinical outcomes.
- Recent research suggests that the results of studies like INSIGHT and ACTION, can only be applied to Adalat<sup>®</sup> GITS – generic long-acting formulations of nifedipine have different pharmacokinetic and pharmacodynamic properties.<sup>5,6</sup>
- Data from a recent bioequivalence study shows that the bioavailability of a generic osmotic release nifedipine was significantly lower compared with Adalat GITS<sup>®</sup>.<sup>7</sup>

### Excellent BP control

- The unique formulation of Adalat<sup>®</sup> GITS provides sustained concentrations of nifedipine over 24 hours, so Adalat<sup>®</sup> GITS only needs to be administered orally once-daily, which helps patients to adhere to therapy. Crucially, the BP-lowering effect associated with Adalat<sup>®</sup> GITS is maintained throughout 24 hours, independent of the time of administration.<sup>8</sup>
- Several large trials, including the Modern Approach to the Treatment of Hypertension (MATH) study,<sup>9</sup> the Extended Release Adalat Canadian Trial (EXACT),<sup>10</sup> and the Shanghai Trial of Nifedipine in the Elderly (STONE),<sup>11</sup> have established the BP-lowering efficacy of Adalat<sup>®</sup>.
- Adalat<sup>®</sup> GITS significantly reduces systolic BP and diastolic BP, and BP targets are achieved in the majority of patients irrespective of age, race or previous antihypertensive therapy.<sup>9-11</sup>



- INSIGHT<sup>2</sup> showed that Adalat<sup>®</sup> GITS significantly reduced BP by 35/17mmHg after 48 months of treatment. During the trial, BP control in patients receiving Adalat<sup>®</sup> GITS monotherapy was equivalent to that achieved in patients receiving diuretic combination therapy (conventional treatment at that time). Additionally, 69% of patients were still receiving Adalat<sup>®</sup> GITS monotherapy at study end.
- In ACTION, Adalat<sup>®</sup> GITS also provided additional BP lowering in high-risk patients with stable coronary artery disease (CAD), reducing BP by 6/3mmHg when Adalat<sup>®</sup> GITS was given on top of best-practice therapy for CAD.<sup>1</sup>
- Patients in the ACTION trial who also had hypertension at baseline achieved a pronounced reduction in BP of 14/7mmHg when receiving Adalat<sup>®</sup> GITS.<sup>12</sup>
- Adalat<sup>®</sup> GITS is also a safe and effective partner for combination with angiotensin-receptor blockers (ARBs), synergistically providing optimal BP control, with potential for additional benefits such as side-effect reduction.<sup>13</sup>
- The combination of Adalat<sup>®</sup> GITS with losartan has been shown to provide significantly greater BP reductions compared with either monotherapy, and with similar tolerability.<sup>14</sup>
- The Nifedipine and Candesartan Combination (NICE Combi)\* study showed that the combination of Adalat<sup>®</sup> and candesartan was superior to up-titrated candesartan monotherapy, with reductions in BP of 13/8mmHg and 5/3mmHg, respectively.<sup>15</sup>
- In the Adalat and Valsartan Cost-effectiveness Combination (ADVANCE-Combi)\* study, Adalat<sup>®</sup> combined with valsartan achieved significantly greater BP reductions than amlodipine and valsartan combined in patients with essential hypertension ( $p < 0.01$ ). Target BP achievement rate was also significantly higher with Adalat<sup>®</sup> (61%) versus amlodipine (35%;  $p < 0.001$ ).<sup>16</sup>
- A Multicentre STudy EvALuating the Efficacy of Nifedipine GITS – Telmisartan Combination in Blood Pressure Control and Beyond: Comparison of Two Treatment Strategies (TALENT) was designed to evaluate the BP-lowering efficacy of initiating combination treatment with Adalat<sup>®</sup> GITS and the ARB telmisartan (Pritor<sup>®</sup>/Kinzal<sup>®</sup>) compared with starting with one drug and adding the second.<sup>17</sup>
- TALENT assessed how to best administer the combination of nifedipine GITS (Adalat<sup>®</sup>) and telmisartan (Pritor<sup>®</sup>/Kinzal<sup>®</sup>) in patients whose BP was uncontrolled or not treated, and who had additional CV risk factors. The trial was also designed to assess the effects of the two treatment strategies on a number of indicators of CV risk.
- TALENT enrolled 405 patients from 40 centers in Italy (30) and Spain (10). Initial findings of the trial were presented at ESH in 2010.
- The Asia Pacific trial – nifedipine in combination with valsartan to achieve blood pressure targets (ADVISE), is a new phase IV, multicenter study evaluating the BP-lowering benefits of combining Adalat<sup>®</sup> GITS/OROS\*\* with the ARB valsartan, in patients with hypertension that are not well-controlled by valsartan monotherapy. ADVISE will enroll 356 patients from China and Korea



(256 in China and 100 in Korea) and began in 2010. Results of the trial are expected in 2011/2012.

\*Study was conducted with nifedipine controlled release formulation (Adalat CR, available only in Japan).

\*\*OROS: Osmotic-controlled Release Oral delivery System. Adalat GITS is marketed as Adalat OROS in the Asia-Pacific region.

### Reduced BP means better outcomes

- It is well-established that achieving a low BP target is associated with CV risk reduction in hypertensive patients.<sup>18</sup> In elderly patients with hypertension, long-acting Adalat<sup>®</sup> has been shown to reduce the relative risk of a CV event by 62% compared with placebo.<sup>11</sup>
- In INSIGHT, Adalat GITS reduced by approximately 50% the predicted risk of a CV event at baseline in patients with hypertension and at least one additional CV risk factor.<sup>2</sup>
- In ACTION, Adalat GITS given in addition to best practice therapy for CAD reduced the risk of death or serious CV events (the composite primary endpoints) by 13% in CAD patients with hypertension at baseline, versus placebo.<sup>12</sup>
- Additionally, Adalat<sup>®</sup> GITS was associated with the following benefits<sup>12</sup>:
  - 38% reduction in new overt heart failure
  - 33% reduction in debilitating stroke
  - 28% reduction in any stroke or transient ischemic attack
  - 16% reduction in coronary angiography.

### Adalat<sup>®</sup> GITS has benefits beyond BP control

- As well as the BP-lowering effects of Adalat<sup>®</sup> GITS, BP-independent mechanisms contribute to prevention of cardiovascular disease (CVD). Many events in the development of atherosclerosis are calcium-dependent, which may explain the additional benefits of Adalat<sup>®</sup> GITS.
- ENCORE I showed that after 6 months of treatment, Adalat<sup>®</sup> GITS increased the lumen diameter of the most constricted segment of the coronary artery in patients with CAD<sup>3</sup> therefore improving endothelial function. This suggests that treatment with Adalat<sup>®</sup> GITS slows the development of atherosclerosis. ENCORE II confirmed that coronary endothelial function was markedly improved following up to 2 years of treatment with Adalat GITS, on top of standard statin therapy.<sup>4</sup>
- Essential hypertension is associated with enhanced endothelin-1 activity and impaired endothelium-dependent vasodilation. Adalat<sup>®</sup> GITS has been shown to improve endothelin-1-dependent vasodilation and endothelial function in the absence of reduced BP; this effect was observed after withdrawal of treatment when BP values had returned to baseline levels.<sup>19</sup>
- Another key step involved in the early progression of CVD is thickening of the artery walls. Adalat<sup>®</sup> GITS has been shown to prevent an increase in intima-media thickness (IMT) in the carotid artery wall compared with diuretic combination therapy despite similar reductions in BP.<sup>20</sup>



### Adalat® GITS targets different stages of the CVD continuum

- In the era of evidence-based medicine and CV risk management, Adalat® GITS has many advantages beyond its excellent BP control:

#### Early phase

- Achieves early and sustained 24-hour BP control
- Improves endothelial function

#### Intermediate phase

- Achieves early and sustained 24-hour BP control
- Reduces progression of atherosclerosis
- Preserves vascular function
- Protects against end-organ damage

#### Late phase

- Achieves early and sustained 24-hour BP control
- Reduces CV risk
- Significantly improves clinical outcomes.

### References

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