

# PITAVASTATIN

## About pitavastatin

- Pitavastatin is a novel, fully synthetic statin that significantly reduces elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TGs)<sup>1</sup>
- Pitavastatin also produces consistent increases in high-density lipoprotein cholesterol (HDL-C) levels, over the short- and long-term<sup>2,3</sup>
- Pitavastatin 4mg has been shown to deliver equivalent coronary plaque volume reduction to atorvastatin 20mg in patients with Acute Coronary Syndrome (JAPAN-ACS)<sup>4</sup>
- Pitavastatin has a novel cyclopropyl group on its base structure, leading to a low potential for CYP3A4 drug-to-drug interactions<sup>2</sup>
- Recently, pitavastatin was shown not to induce diabetes when administered to Japanese patients with impaired glucose tolerance<sup>5</sup>

## Indication

Pitavastatin is indicated for the reduction of elevated TC and LDL-C in adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, and combined (mixed) dyslipidaemia, when response to dietary and other non-pharmacological measures are inadequate.<sup>1</sup>

## Dosing

Pitavastatin is available in three strengths: 1mg, 2mg and 4mg.<sup>1</sup>

The usual starting dose is 1mg once daily. Most patients will require a 2mg dose. The maximum daily dose is 4mg.<sup>1</sup>

Pitavastatin can be taken at any time of the day with or without food, allowing flexibility for patients.<sup>1</sup>

## Pitavastatin structure

Pitavastatin's novel chemical structure has the following consequences:

- Minimal metabolism - pitavastatin is only minimally metabolised by the liver through the cytochrome P450 pathway, a common pathway for the metabolism of many other medications.<sup>6</sup> Pitavastatin's lack of metabolism in the gut probably contributes to its high bioavailability<sup>2</sup>
- Low potential of interactions - due to its lack of metabolism by CYP, pitavastatin has a low potential for CYP3A4-mediated drug-to-drug interactions<sup>3</sup>

Pitavastatin's low potential for CYP3A4-mediated drug-to-drug interactions makes it an option for patients who are on multiple medications<sup>2</sup> and/or who are receiving anti-retroviral therapy (ART) for the treatment of HIV (Human Immunodeficiency Virus).<sup>1</sup> ART is known to increase the risk of impaired glucose tolerance and dyslipidaemia; putting patients at increased risk of cardiovascular disease (CVD).<sup>7-9</sup>

## Phase III clinical studies

- Pitavastatin effectively reduced LDL-C and achieved European Atherosclerosis Society (EAS) guideline targets in the majority of patients with primary hypercholesterolaemia or combined dyslipidaemia, similar to reductions seen with atorvastatin<sup>10</sup> and simvastatin<sup>11</sup> after 12 weeks of treatment
- Pitavastatin 2mg was statistically significantly superior compared with simvastatin 20mg in lowering LDL-C, non-HDL-C and TC after 12 weeks of treatment<sup>11</sup>
- Pitavastatin effectively reduced LDL-C in the elderly<sup>12</sup> and also improved LDL-C and other parameters of lipid metabolism in patients at high cardiovascular risk<sup>2</sup>
- Pitavastatin was statistically significantly superior to pravastatin in improving LDL-C at all dose comparisons in elderly patients (≥65 years) after 12 weeks of treatment<sup>2,12</sup>
- Pitavastatin 4mg demonstrated a gradual and sustained increase in HDL-C over the long-term, supported by data from a 52 week extension study<sup>3</sup>

## Quick facts

- Pitavastatin is a fully synthetic, novel statin<sup>2</sup>
- Pitavastatin's cyclopropyl group on the base structure allows for minimal metabolism and low risk of CYP3A4 mediated drug-to-drug interactions<sup>2,8</sup>
- Pitavastatin's safety and tolerability are comparable to other commonly prescribed statins<sup>4,6,7</sup>
- Pitavastatin does not appear to increase the risk of developing diabetes in Japanese subjects<sup>5</sup>
- Pitavastatin has been granted approval in a number of countries-Europe, Asia, South America and USA

## Safety and tolerability

The overall safety and tolerability of pitavastatin is consistent with other commonly prescribed statins. In pivotal clinical studies, pitavastatin demonstrated:

- Low incidence of adverse events (AEs)
  - In Phase III studies comparing pitavastatin with atorvastatin,<sup>10</sup> simvastatin<sup>11</sup> and pravastatin<sup>2</sup> over 12 weeks, the comparable tolerability profile of pitavastatin was demonstrated, with a low incidence of AEs
- Comparable tolerability
  - In patients with primary hypercholesterolaemia or combined dyslipidaemia, pitavastatin demonstrated a similar tolerability profile to atorvastatin and simvastatin respectively, at comparable therapeutic doses<sup>10,11</sup>
  - All three doses of pitavastatin (1, 2 and 4mg) demonstrated a comparable tolerability profile to 10, 20 and 40mg of pravastatin over 12 weeks<sup>12</sup>
  - In patients with primary hypercholesterolaemia or combined dyslipidaemia, pitavastatin demonstrated long-term tolerability (52 weeks) with no serious treatment-emergent adverse event (TEAEs) being attributed to pitavastatin<sup>2,3</sup>
- Long-term safety profile
  - Pitavastatin has demonstrated a long-term safety profile (to 52 weeks),<sup>3</sup> comparable to that of simvastatin or atorvastatin<sup>13,14</sup>
  - Furthermore, the two year follow-up in a post-marketing surveillance study conducted in nearly 20,000 patients in Japan showed a low incidence of overall AEs, the majority of which were mild. Serious adverse reactions were rare; with only two reports of rhabdomyolysis requiring hospitalisation (0.01% of patients)<sup>1</sup>
- Risk of diabetes
  - Some evidence suggests that statins as a class raise blood glucose and in some patients at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk of hyperglycaemia (fasting glucose 5.6 to 6.9mmol/L, BMI>30kg/m<sup>2</sup>, raised TGs, hypertension), should be monitored both clinically and biochemically according to national guidelines<sup>15</sup>
  - The only prospective trial to evaluate the effect of a statin on the development of diabetes was published in 2013<sup>5</sup>
  - Results showed that pitavastatin did not increase the risk of diabetes among Japanese patients with impaired glucose tolerance after a median of 2.8 years<sup>5</sup>

## Approval

Pitavastatin was first launched in Japan in 2003 and launched around the world including China and the USA.

Pitavastatin achieved a positive outcome from the UK Regulatory Authority (MHRA) acting as the Reference Member State for 16 European Union countries in 2010<sup>15</sup> and subsequently it has been approved and launched in many EU countries.

1. Kowa Pharmaceuticals Europe Co. Ltd. Consolidated Summary of Product Characteristics, Pitavastatin 1mg, 2mg & 4mg film-coated tablets. 2. Ose L. Pitavastatin: finding its place in therapy. *Ther Adv Chronic Dis* 2011. Published online before print. January 26, 2011, doi: 10.1177/2040622310389227. 3. Ose L, et al. Long-term treatment with pitavastatin is effective and well tolerated by patients with primary hypercholesterolemia or combined dyslipidemia. *Atherosclerosis* 2010; 210(1): 202-208. 4. Hiro T, et al. Effect of intensive statin therapy on regression of Coronary Atherosclerosis in patients with acute coronary syndrome. *J Am Coll Cardiol* 2009; 54: 293-302. 5. Odawara M, et al. European Association for the Study of Diabetes 2013. Abstract 128. Available at <http://www.easdvirtualmeeting.org/resources/3645>. Accessed November 2013. 6. Mukhtar RYA, et al. Pitavastatin. *Int J Clin Pract* 2005; 59(2): 239-252. 7. Dube MP. Disorders of Glucose Metabolism in Patients Infected with Human Immunodeficiency Virus. *Clin Infect Diseases* 2000; 31: 1467-1475. 8. Riddler SA, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003; 289(22): 2978-2982. 9. Dube MP, et al. Guidelines for the Evaluation and Management of Dyslipidemia in Human Immunodeficiency Virus (HIV)-Infected Adults Receiving Antiretroviral Therapy: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Diseases* 2003; 37: 613-627. 10. Budinski D, et al. Pitavastatin compared with atorvastatin in primary hypercholesterolemia or combined dyslipidemia. *Clin Lipidol* 2009; 4(3): 291-302. 11. Ose L, et al. Comparison of pitavastatin with simvastatin in primary hypercholesterolaemia or combined dyslipidaemia. *Curr Med Res Opin* 2009; 25(11): 2755-2764. 12. Stender S, Hounslow N. Robust efficacy of pitavastatin and comparable safety to pravastatin. *Atherosclerosis Suppl* 2009; 10(2): e945. 13. Data on file (study 305). 14. Data on file (study 310). 15. Medicines and Healthcare products Regulatory Agency Public Assessment Report. Available at <http://www.mhra.gov.uk/home/groups/par/documents/websitesresources/con096843.pdf>. Accessed November 2013.