Kowa Pharmaceutical Europe Co. Ltd.

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)[1]
- Pitavastatin also produces consistent increases in high-density lipoprotein cholesterol (HDL-C) levels, over the short- and long-term[2,3]
- Pitavastatin 4mg has been shown to deliver equivalent coronary plaque volume reduction to atorvastatin 20mg in patients with Acute Coronary Syndrome (JAPAN-ACS)[4]
- Pitavastatin has a novel cyclopropyl group on its base structure, leading to a low potential for CYP3A4 drug-to-drug interactions[2]
- Recently, pitavastatin was shown not to induce diabetes when administered to Japanese patients with impaired glucose tolerance[5]

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.[1]

Dosing

Pitavastatin is available in three strengths: 1mg, 2mg and 4mg.[1]

The usual starting dose is 1mg once daily. Most patients will require a 2mg dose. The maximum daily dose is 4mg.[1]

Pitavastatin can be taken at any time of the day with or without food, allowing flexibility for patients.[1]

Quick facts

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

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.[6] Pitavastatin's lack of metabolism in the gut probably contributes to its high bioavailability[2]
- Low potential of interactions – due to its lack of metabolism by CYP, pitavastatin has a low potential for CYP3A4-mediated drug-to-drug interactions[3]

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

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[10] and simvastatin[11] 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[11]
- Pitavastatin effectively reduced LDL-C in the elderly[12] and also improved LDL-C and other parameters of lipid metabolism in patients at high cardiovascular risk[2]
- 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[2,12]
- Pitavastatin 4mg demonstrated a gradual and sustained increase in HDL-C over the long-term, supported by data from a 52 week extension study[3]

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,[10] simvastatin[11] and pravastatin[2] 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[10,11]
  - All three doses of pitavastatin (1, 2 and 4mg) demonstrated a comparable tolerability profile to 10, 20 and 40mg of pravastatin over 12 weeks[12]
  - 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[2,3]
- Long-term safety profile
  - Pitavastatin has demonstrated a long-term safety profile (to 52 weeks),[3] comparable to that of simvastatin or atorvastatin[13,14]
  - 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)[1]
- 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^2, raised TGs, hypertension), should be monitored both clinically and biochemically according to national guidelines[15]
  - The only prospective trial to evaluate the effect of a statin on the development of diabetes was published in 2013[5]
  - 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[5]

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[15] 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/websiteresources/con096843.pdf. Accessed November 2013.

PIT13 00022 Date of preparation: November 2013