



## KOWA Pharmaceuticals - Q&A

This question and answer (Q&A) document has been developed to assist official Kowa Pharmaceuticals spokespeople/Ruder Finn in answering questions from key stakeholders, including the media.

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## Kowa Company Ltd

**Q1.** Who is Kowa Pharmaceuticals Europe?

- Kowa Pharmaceuticals Europe Co. Ltd (KPE) is a wholly owned subsidiary of Kowa Company Ltd established in 2000 in the United Kingdom. KPE is responsible for the European, and Middle East and North Africa pharmaceutical marketing of Kowa products.
- Kowa Company Ltd is one of the largest privately owned companies in Japan and was first established in 1894. It has since grown into a multinational company. Kowa Company Ltd is engaged in various manufacturing and trading activities in the fields of pharmaceutical, life science and information technology, textiles, machinery and various consumer products.

**Q2.** When was Kowa Pharmaceuticals Europe founded?

- Kowa Pharmaceuticals Europe was established in 2000 in the United Kingdom.

**Q3.** What products does Kowa currently have in development?

- Kowa has a range of pharmaceutical compounds in development:
  - Pitavastatin, for the treatment of dyslipidaemia, has launched in five countries and has been approved in many European countries.
  - Oral peretinoin has been filed for approval in Japan for the prevention of recurrent of liver cancer.
  - SK-0403(oral), a dipeptidyl peptidase 4 (DPP-4) inhibitor, is currently undergoing phase III clinical trials in Japan and phase II clinical trials in the USA for the treatment of type 2 diabetes mellitus.
  - K-134 (oral), an antiplatelet agent, is currently undergoing phase II clinical trials in Japan and the USA for the treatment of arteriosclerosis obliterans.
  - K-604 (oral), an ACAT-1 inhibitor, is currently undergoing phase II clinical trials in the USA for the treatment of atherosclerosis.
  - K-115 (eye drop), a rho kinase inhibitor, is currently undergoing phase II clinical trials in Japan for the treatment of glaucoma and ocular hypertension.
  - K-877 (oral), a PPAR- $\alpha$  agonist, is currently undergoing phase II clinical trials in Japan for the treatment of dyslipidaemia.
  - K-828-AB (oral), a GABA transaminase Inhibitor, is currently undergoing phase II clinical trials in Japan for the treatment of behavioural and psychological symptoms of dementia.

**Q4.** Does Kowa Pharmaceuticals plan to develop and market treatments only for cardiovascular disease/conditions?

- No, Kowa Pharmaceuticals is developing and marketing treatments for the prevention of recurrent liver cancer, type 2 diabetes, glaucoma and ocular hypertension and the treatment of behavioural and psychological symptoms of dementia. Kowa Pharmaceuticals is also developing treatments in the cardiovascular area for dyslipidaemia, arteriosclerosis obliterans and atherosclerosis.

### About pitavastatin

Q5. What is pitavastatin?

- Pitavastatin is a fully synthetic and highly potent HMG-CoA reductase inhibitor (statin).

Q6. What is pitavastatin indicated for?

- Pitavastatin is indicated for the reduction of elevated total cholesterol (TC) and low density lipoprotein cholesterol (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>

Q7. Which patients are eligible for pitavastatin?

- Adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, and combined (mixed) dyslipidaemia, when response to dietary and other non-pharmacological measures are inadequate are eligible for pitavastatin.<sup>1</sup>
- Pitavastatin may also be an appropriate first-line treatment option for clinically complex patients, such as:
  - Patients with impaired renal (kidney) function
  - Patients with mild to moderate impaired hepatic (liver) function
  - Patients taking multiple medications, because the route of metabolism of the drug is thought to be less likely to result in an interaction with other drugs
  - Elderly patients
  - Patients with concomitant diseases affecting drug metabolism.

Q8. What are the recommended doses for pitavastatin?

- Pitavastatin is available in three recommended low-dose strengths, including: 1 mg, 2 mg and 4 mg. The usual starting dose is 1 mg once daily, but most patients will require a 2 mg dose.<sup>1</sup>
- Adjustment of dose should be made at intervals of four weeks or more, and individualised according to the patients' LDL-C levels, the goal of therapy and patient response. The maximum daily dose is 4 mg.<sup>1</sup>

Q9. Are there different doses available in different markets?

- There are different doses available in different markets including:
  - In the USA, the usual starting dose is 2 mg, although patients may derive increased benefit from a dose of 4 mg.<sup>2</sup>
  - In Europe, the usual starting dose is 1 mg, although most patients will require a 2 mg dose. The maximum dose of pitavastatin available is 4 mg.<sup>1</sup>

**Q10.** Are all doses of pitavastatin safe and efficacious?

- Yes, clinical trials demonstrate that 1 mg, 2 mg and 4 mg doses of pitavastatin are safe and efficacious.
  - Pitavastatin 1 mg 2 mg and 4 mg are effective in lowering LDL-C, and are non-inferior compared to low to medium-range doses of simvastatin, atorvastatin and pravastatin and even superior in the case of pravastatin (pravastatin 80mg was not tested).<sup>2</sup>
  - Clinical data demonstrate that 1 mg, 2 mg and 4 mg doses of pitavastatin are not associated with increased risk for myopathy above those of low-to-moderate doses of simvastatin, atorvastatin and pravastatin.<sup>2</sup>
  - Although there is a greater incidence of transaminitis in subjects treated with 1 mg, 2 mg and 4 mg of pitavastatin compared with those of low-to-moderate doses of simvastatin, atorvastatin and pravastatin, it was noted that this is unlikely to be of clinical significance.<sup>2</sup>

**Q11.** How is pitavastatin administered?

- Pitavastatin is an oral treatment taken once daily at any time of the day, with or without food. It is desirable that patients take pitavastatin at the same time each day.<sup>1</sup>

**Q12.** How does pitavastatin differ from other currently available statins?

- Pitavastatin has a unique cyclopropyl group on the base structure,<sup>4</sup> which provides:
  - A more effective inhibition of the HMG-CoA reductase enzyme to inhibit cholesterol production, which potentially affords greater LDL-C clearance and reduction of plasma cholesterol.
  - Minimal metabolism by the cytochrome P450 pathway in the liver, a common pathway for the metabolism of many other medications.<sup>4</sup>
  - Reduced risk of interactions as it does not interact with agents that inhibit or induce CYP3A4, markedly reducing the risk of drug-to-drug<sup>3</sup> and drug-to-food interactions compared with some other statins, such as simvastatin, lovastatin and atorvastatin.<sup>10</sup>

**Q13.** Pitavastatin is the seventh statin to market, is there a need for another statin?

- Pitavastatin differs from other currently marketed statins as it has a unique cyclopropyl group on the base structure.<sup>4</sup> This cyclopropyl group contributes to:
  - A more effective inhibition of the HMG-CoA reductase enzyme to inhibit cholesterol production, and allows the use of a lower dose.
  - Minimal metabolism by the cytochrome P450 pathway in the liver, through which many other medications are metabolised.<sup>4</sup>
  - Reduced risk of drug-to-drug and drug-to-food interactions with agents compared with some other statins, such as simvastatin, lovastatin and atorvastatin.<sup>10</sup>
- Kowa Pharmaceuticals is confident that pitavastatin will benefit adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, and combine (mixed) dyslipidaemia, when response to dietary and other non-pharmacological measures are inadequate.
- The low drug-to-drug interaction may be a potential opportunity for clinically complex patients on multiple medications.<sup>4</sup>

### Clinical trial data

#### Q14. What data are available for pitavastatin?

- A growing number of studies, including a large clinical programme in Europe, Russia, India and Israel, show that pitavastatin is clinically efficacious in the management of primary hypercholesterolemia or combined dyslipidaemia in a wide range of patients.
- Pivotal Phase III clinical trials demonstrated that:
  - Pitavastatin safely and effectively reduced LDL-C and achieved European Atherosclerosis Society (EAS) guideline targets in the majority of patients with primary hyperlipidemia or mixed dyslipidemia, similar to reductions seen with atorvastatin<sup>5</sup> and simvastatin.<sup>6</sup>
  - Pitavastatin 2 mg and 4 mg demonstrated comparable efficacy to commonly prescribed statins with 2 mg pitavastatin demonstrating statistically significant superior efficacy compared with simvastatin 20 mg in lowering LDL-C, non high-density lipoprotein cholesterol (non-HDL-C) and total cholesterol (TC).<sup>6</sup>
  - Pitavastatin effectively reduced LDL-C and improved other parameters of lipid metabolism in special patient populations including the elderly<sup>7</sup> and patients at higher cardiovascular risk.<sup>4</sup>
  - Pitavastatin was superior to pravastatin in improving TC and LDL-C in elderly patients (65 years).<sup>7</sup>
  - Pitavastatin demonstrated a gradual and sustained increase in high-density lipoprotein cholesterol (HDL-C) over the long-term, supported by data from a 52 week extension study.<sup>8</sup>
- In the two year post-marketing surveillance study (LIVES), which involved more than 20,000 patients in Japan, pitavastatin demonstrated that the majority of adverse events were mild. Adverse event rates were higher over 2 years in patients with a history of drug allergy (20.4%), or hepatic renal disease (13.5%).<sup>1</sup>

#### Q15. How many patients has pitavastatin been studied in?

- Since its 2003 launch in Japan, pitavastatin has accumulated millions of patient-years of exposure.
- Large scale clinical trials have been carried out in Europe, Russia, India and Israel, which show that pitavastatin is clinically efficacious in the management of primary hypercholesterolemia or combined dyslipidaemia in a wide range of patients.

#### Q16. What were the primary endpoints for phase III clinical trials and were they met?

- Overall, Phase III studies demonstrated that pitavastatin 1 mg, 2 mg and 4 mg is well tolerated and was shown to improve atherogenic lipid profile and increase LDL-C target attainment rates with a similar or greater efficacy to comparable doses of atorvastatin, simvastatin and pravastatin in most patient groups.
- Phase III studies conducted in Europe included five 12-week, randomised, double-blind trials evaluating the non-inferiority of pitavastatin 1 mg, 2 mg and 4 mg vs. atorvastatin 10-20 mg, simvastatin 20-40 mg and /or pravastatin 10-40 mg in patients with primary hypercholesterolaemia and combined dyslipidaemia, including patients with high cardiovascular risk, type II diabetes, and age ≥65 years.
- In each of the studies, improvements in lipid profile were sustained or improved during the long term suggesting benefits for continued treatment with pitavastatin.

## Safety and adverse events

**Q17.** What is the safety profile of pitavastatin?

- The overall safety of pitavastatin is consistent with other commonly prescribed statins.
- In Phase III clinical trials comparing pitavastatin with atorvastatin,<sup>5</sup> simvastatin<sup>6</sup> and pravastatin<sup>7</sup>, the overall safety profile of pitavastatin was demonstrated, with low incidences of adverse events.

**Q18.** What adverse events have been observed in pitavastatin trials to date?

- Overall, the majority of adverse events observed in clinical trials have been mild and adverse event rates did not increase with dose.
- In clinical trials, the most common adverse reactions (incidence  $\geq 2\%$ ) were: back pain, constipation and diarrhoea, myalgia and pain in extremities.<sup>9</sup>
- In a prospective post-marketing surveillance study in Japan of nearly 20,000 patients, results showed:<sup>1</sup>
  - 10.4% of patients reported adverse events for which a causal relationship to pitavastatin could not be ruled out.
  - 7.4% of patients withdrew from therapy due to adverse events.
  - The myalgia rate was 1.08%.
- Adverse event rates were higher over 2 years in patients with a history of drug allergy (20.4%), or hepatic or renal disease (13.5%).<sup>1</sup>

**Q19.** Were there any severe adverse events observed?

- In the post-marketing surveillance study there were two reports of rhabdomyolysis requiring hospitalisation (0.001% of patients).<sup>1</sup>

**Q20.** Has Kowa Pharmaceuticals observed any drug-to-diet interactions with pitavastatin?

- Pitavastatin's drug-to-diet interactions are markedly reduced compared to some other statins, such as simvastatin, lovastatin and atorvastatin.
- Pitavastatin's does not interact with agents that inhibit or induce CYP3A4. In one trial, co-administration of grapefruit juice (a known CYP3A4 inhibitor) produced no clinically relevant effect on the pharmacokinetics of pitavastatin.<sup>10,11</sup>
- No other drug-to-diet interactions have been observed in clinical trials with pitavastatin.

**Q21.** Has Kowa Pharmaceuticals observed any drug-to-drug interactions with pitavastatin?

- Pitavastatin has a reduced risk of drug-to-drug interactions compared with other statins, such as simvastatin, lovastatin and atorvastatin.<sup>10</sup>
- Pitavastatin does not interact with agents that inhibit or induce CYP3A4. One clinical trial demonstrated that the co-administration of itraconazole (a known CYP3A4 inhibitor) produced no clinically relevant effect on the pharmacokinetics of pitavastatin or the lactone metabolite.<sup>10,11</sup>
- Significant pharmacokinetic interactions with pitavastatin have been observed with ciclosporin and co-administration with pitavastatin is contraindicated.<sup>1</sup>

**Q21. (Continued)**

- Pharmacokinetic interactions of pitavastatin with erythromycin have been observed, and a temporary suspension of pitavastatin is recommended for the duration of treatment with erythromycin or other macrolide antibiotics.<sup>1</sup>
- Gemfibrozil and other fibrates (drugs used for the treatment of dyslipidaemia) have demonstrated slight pharmacodynamic interaction with pitavastatin. Concomitant use of pitavastatin with either fenofibrate or gemfibrozil should be administered with caution (though are not contraindicated).<sup>1</sup>
- Other minor interactions observed include: niacin, fusidic acid, rifampicin, protease inhibitors, ezetimibe, digoxin and warfarin.<sup>1</sup>

**Q22. Can pitavastatin be taken safely in pregnant or breastfeeding women?**

- No, like other currently available statins, pitavastatin is contraindicated in women who are pregnant or breastfeeding. It must not be prescribed to pregnant or breastfeeding women and should be discontinued before conception in women intending to become pregnant.<sup>1</sup>
- Women of child bearing potential must take appropriate contraceptive precautions during treatment of pitavastatin.<sup>1</sup>

**Regulatory**

**Q23. What is the status of pitavastatin's regulatory approval in Europe?**

- Pitavastatin achieved a positive outcome from the UK Regulatory Authority (MHRA) acting as the Reference Member State for 16 European Union countries in July 2010.<sup>12</sup>

**Q24. What is the status of pitavastatin's regulatory approval in the USA?**

- Pitavastatin was approved in the USA in August 2009 and is indicated for the treatment of primary hypercholesterolaemia and combined dyslipidaemia and launched in June 2010.<sup>9</sup>

**Q25. What is the status of pitavastatin's regulatory approval in Asia-pacific?**

- Pitavastatin was approved in Japan in September 2003, Korea in July 2005, Thailand in January 2008 and China in July 2009.

**Q26. In what markets has pitavastatin launched?**

- Pitavastatin launched in Japan in 2003, South Korea in 2005, Thailand in 2008, China in 2009, USA in 2010, Lebanon in 2011 and parts of Europe.
- Pitavastatin has been successfully used in these countries to treat primary hypercholesterolaemia and combined dyslipidaemia.

## Marketing

- Q27.** How much does pitavastatin cost in the markets where it has launched?
- Pitavastatin is priced competitively alongside leading statins in the marketplace.
- Q28.** Will the cost of pitavastatin differ in future markets?
- Kowa's pricing strategy is not yet finalised and approved. Kowa anticipate that pitavastatin will be priced competitively alongside leading statins in the marketplace.
- Q29.** What is the anticipated market size (sales forecast) for pitavastatin?
- The anticipated market size (sales forecast) for pitavastatin is currently undisclosed.
  - The annual sales of pitavastatin in Japan reached \$520 million in 2010.
- Q30.** What are Kowa's marketing and distribution plans for pitavastatin?
- Kowa has licensed pitavastatin to a number of different companies in different countries. It has licensed the primary marketing rights to Recordati in many European markets. Kowa will distribute pitavastatin in UK and Germany. Solvay Canada Inc will distribute the product in Canada. Algorithm SAL will distribute the product in the Middle East and North Africa. Abbott has recently been given an exclusive license to distribute and market pitavastatin in Australia and New Zealand.

## Statins

- Q31.** What are statins?
- Statins (or HMG-CoA reductase inhibitors) regulate the level of cholesterol in the body by:
    - Blocking the enzyme that produces cholesterol in the liver
    - Helping lower low density lipoprotein-cholesterol (LDL-C) and triglycerides (TGs)
    - Mildly assisting in raising high density lipoprotein-cholesterol (HDL-C).
- Q32.** How widely are statins used?
- Statins are widely and increasingly used in most European countries. Despite the availability and known safety profile of statins, there is still a need for better control of and treatment for dyslipidaemia:
    - Only 51% of patients on lipid lowering therapy were achieving the treatment goals of the European guidelines.<sup>13</sup>
- Q33.** What are the most common side effects associated with using statins?
- Statins are generally very well tolerated and many people taking them will not experience any side effects. However, as with all medications there are a number of side effects which will affect a varying number of people, to a varying degree. The following adverse events have been reported with some statins: sleep disturbances, including nightmares, memory loss, sexual dysfunction, depression and exceptional cases of interstitial lung disease, especially with long term therapy.<sup>1</sup>

**Q34.** What other novel agents are currently on the market or in development?

- There are a number of lipid modifying treatments currently available, including:
  - Statins: simvastatin (Zocor<sup>®</sup>, MSD, and generic), rosuvastatin (Crestor<sup>®</sup>, AstraZeneca), atorvastatin (Lipitor<sup>®</sup>, Pfizer), fluvastatin (Lescol<sup>®</sup>, Novartis), lovastatin (generic) and pravastatin (Lipostat<sup>®</sup>, BMS).
  - Fibrates, which are a class of medication that increase HDL-C levels and decrease triglyceride levels. Fibrates are often used in combination with statins.
  - Ezetrol<sup>®</sup> (ezetimibe), which works by preventing cholesterol from being absorbed from the small intestine into the blood.
  - Niacin helps reduce triglycerides and LDL-C and improves HDL-C levels.
  - Cholesterylester transfer protein (CETP) inhibitors are in development. They block the release of cholesterol from HDL particles, increase HDL-C levels, and prevent development of LDL.

#### About dyslipidaemia/hypercholesterolaemia

**Q35.** What is cholesterol?

- Cholesterol is a type of fat produced in the liver. It is present in all human cells and forms part of the cell membrane. Cholesterol is also a constituent of various hormones in the body. There are two key types of cholesterol:
  - LDL-C also known as ‘bad’ cholesterol can lead to coronary heart disease (CHD) and stroke.
  - HDL-C also known as ‘good’ cholesterol helps carry excess cholesterol out of the blood to the liver and removed from the body.
- Excess calories, alcohol or sugar in the body are converted into TGs. TGs are another type of fat present in the blood. Excess TGs are transported by the very low-density lipoprotein (VLDL).

**Q36.** What are dyslipidaemia and hypercholesterolaemia?

- Dyslipidaemia is a general term that refers to abnormal levels of fat in the blood, characterised high TC, including high levels LDL-C and TGs, and by reduced levels of HDL-C.
- An elevated level of cholesterol in the blood is called hypercholesterolaemia, commonly referred to as high cholesterol. Patients with high cholesterol and abnormalities of blood fats, particularly high levels of LDL-C and low levels of HDL-C are at increased risk of heart disease and stroke.

**Q37.** How common are dyslipidaemia and hypercholesterolaemia?

- Dyslipidaemia/hypercholesterolaemia is common, affecting an estimated 55-70% of adults in Europe.

**Q38.** How are dyslipidaemia and hypercholesterolaemia diagnosed?

- Dyslipidaemia and hypercholesterolaemia are diagnosed by measuring plasma levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs).

**Q39.** How are dyslipidaemia and hypercholesterolaemia treated?

- Treatments for dyslipidaemia and hypercholesterolaemia include lifestyle modifications including diet and exercise, and lipid-lowering medications, such as statins, particularly for lowering LDL-C.

**Q40.** What are the causes of dyslipidaemia and hypercholesterolaemia?

- Risk factors for dyslipidaemia include obesity, medications, hypothyroidism, a high-fat diet, inactivity, and smoking. Dyslipidaemia can also be caused by several inherited genetic disorders .

**Q41.** What are the consequences on health of dyslipidaemia and hypercholesterolaemia?

- Dyslipidaemia and hypercholesterolaemia increase the risk of heart disease, stroke or a heart attack, particularly in high-risk patients such as those with diabetes or who have a family history of heart disease.

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