JAPAN

Inventive step related to dosage and administration

ABE & Partners
Osaka

Takanori Abe and Isamu Kotobuki

Zoledronic acid hydrate (zoledronate) is a medicinal compound created by Novartis and is also an active substance of the bone resorption inhibitor named Zometa for i v infusion. Novartis filed a Japanese patent application including the claimed invention as follows: "An agent for treatment containing 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid (Zoledronate) or pharmaceutically acceptable salts, wherein 4 mg of Zoledronate is to be administered intravenously over a period of 15 minutes to a patient in need of bisphosphonate treatment."

JPO

Both the inventions stated in D1 and the claimed invention are commonly agents for treatment containing 4mg of zoledronate to be administered intravenously within certain minutes. However, "five-minute" corresponds to "certain minutes" in D1, whereas "fifteen-minute" is mentioned in the claimed invention.

D3 discloses that the slow administration of bisphosphonate with large quantities of liquid is preferred for preventing the renal insufficiency caused by its prompt administration. D2 discloses that zoledronate used to be administered intravenously within five to 30 minutes and its 20-minute administration causes a serum calcium lowering effect. Thus, making the five-minutes of the intravenous administration time slow, and arriving at 15 minutes, was merely an exercise for skilled persons to do experimentally.

IP High Court

In the judgment of December 24 2014, the IP High Court (Presiding Judge Tomita) rescinded the JPO's decision.

D2 is a document explaining phase I clinical trials using zoledronate for tumour-induced hypercalcemia patients and so on. D1 is a document explaining phase II clinical trials using it for multiple myeloma patients and breast cancer patients. The result of phase III clinical trials using it for breast cancer patients or multiple myeloma patients was published after the filing of the patent application.

Zoledronate indicating an action to suppress the function of osteoclasts is the third-generation bisphosphonate. The results of phase I clinical trials stated in D2 reveal that zoledronate works more promptly than the other bisphosphonates and indicate the prolonged serum calcium lowering effects and any symptoms of renal toxicities are not shown in the osteolytic bone metastasis patients who have a normal calcium plasma and are administered intravenously 0.1mg to 8mg of zoledronate within five minutes. The results suggest that the short-time intravenous administration of zoledronate would be safe. Furthermore, the subsequent phase II clinical trials stated in D1 also reveal that the safety of the five-minute intravenous administration of "0.4mg, 2mg or 4mg of zoledronate" to breast cancer patients and multiple myeloma patients is comparable to that of the two-hour intravenous administration of 90mg of pamidronate, and the preventive effects caused by the five-minute intravenous administration of 4mg of zoledronate to osteolytic bone complication patients are comparable to those of the two-hour intravenous administration of 90mg of pamidronate.

According to the above disclosure in D1 and D2, skilled persons can easily understand that the low amount of 4mg of zoledronate causes the medicinal effects comparable to 90mg of pamidronate, and short-time five-minute intravenous administration confirms the safety.

The results of such clinical trials indicate no result that raises a doubt about safety at the stage of phase I and phase II clinical trials, even taking into account the existence of the possibility that dosage and administration will be changed to safer levels as a result of a phase III trial showing a different result concerning the safety of said dosage and administration in consideration of the stepwise nature of clinical trials. Therefore, even from the perspective of convenience for and reduction of burden on patients, it is difficult to find a motivation to further extend "five-minute" in D1 to "fifteen-minute" by D1 and D2.

According to the background to development of second- and third-generation bisphosphonate and actual results of prompt administration at the time of the priority date, skilled persons could understand that knowledge about adverse events to the kidney caused by prompt administration of first-generation bisphosphonate, which is stated in D3, is not immediately applicable to zoledoronate, which is the third-generation bisphosphonate.

Taking into account that zoledoronate is a bisphosphonate which is 100 to 850 times as highly active as pamidronate and that it has a higher bone resorption inhibiting effect than incadronate and alendronate and its administration in a small dose suffices, it is also difficult to find a motivation to further extend the administration time, that is, five-minute administration of 4 mg of zoledoronate, of which safety was confirmed in D1 and D2, from the perspective of convenience for and reduction of burden on patients.

Practical tips

In 2009, the JPO examination guideline was revised to permit dosage/administration claims. However, dosage/administration claims for solving problems such as reduction of adverse effect usually lack inventive step according to this guideline. As the claim is directed to the reduction of adverse effect in the kidney, the inventive step could be denied according to the guideline. The JPO actually rejected the claim.

However, the IP High Court found no motivation to further extend the administration time existing because adverse effect in kidney caused by 4mg/five minutes administration was not recognised by the skilled person. Recently, the courts have held that the problem to be

solved should be easily set when rejecting the application due to lack of inventive step. This judgment is in line with this tendency. If the invention is directed to the reduction of adverse effects, it is important for the applicants to prove that the problem to be solved is not well-known as is stated in the JPO examination guideline.