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R&D INSIGHT REPORT

Vonoprazan: First Global Approval

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Abstract Vonoprazan (Takecab®) is an orally bioavailable potassium-competitive acid blocker (P-CAB) being developed by Takeda for the treatment and prevention of acid-related diseases. The drug is approved in Japan for the treatment of acid-related diseases, including erosive oesophagitis, gastric ulcer, duodenal ulcer, peptic ulcer, gastro-oesophageal reflux, reflux oesophagitis and *Helicobacter pylori* eradication. Phase III development is underway for the prevention of recurrence of duodenal and gastric ulcer in patients receiving aspirin or NSAID therapy. Phase I development was conducted in the UK for gastro-oesophageal reflux; however, no further development has been reported. This article summarizes the milestones in the development of vonoprazan leading to this first approval for acid-related diseases.

1 Introduction

The major target in the pharmacological treatment of acid-related diseases is the gastric proton pump enzyme H^+, K^+-ATPase [1]. The two main classes of drug that target this enzyme are proton-pump inhibitors (PPIs; e.g. lansoprazole) and potassium-competitive acid blockers [P-CABs; e.g. oral vonoprazan (Takecab®)] [1]. PPIs bind irreversibly to the enzyme by forming a covalent complex at specific cysteine residues; P-CABs reversibly inhibit gastric acid secretion by competing with the K^+ on the luminal surface [1, 2]. PPIs have a delayed onset of acute effect, achieving full effect over several dose cycles; thus, many patients prefer P-CABs as an alternative, as they rapidly reach high plasma concentrations and are associated with a fast onset of action [2]. However, the binding to H^+, K^+-ATPase by some classes of P-CABs is reversed rapidly, leading to reduced efficacy of once-daily dosing [3]. Thus, vonoprazan was developed, with a comparatively slow off-rate [3].

In December 2014, the Japanese Ministry of Health, Labour and Welfare approved vonoprazan for the treatment of adult patients with acid-related diseases, including gastric ulcer, duodenal ulcer, reflux oesophagitis, and the prevention of recurrence of gastric or duodenal ulcer during low-dose aspirin or non-steroidal anti-inflammatory drug (NSAID) administration, as well as an adjunct to *Helicobacter pylori* eradication in patients with gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, *H. pylori* gastritis, and after endoscopic resection of early-stage gastric cancer [4]. The approval was granted on the basis of favourable outcomes from multiple phase III trials conducted in Japan [4]. The new drug application for approval of vonoprazan was filed by Takeda in February 2014 [5].

Vonoprazan is administered orally; the dosage and duration are dependent on the indication [4]. In patients with gastric or duodenal ulcer, the usual dosage is 20 mg once daily for 8 or 6 weeks, respectively. For the prevention of recurrence of gastric or duodenal ulcer during low-dose aspirin or NSAID use, the usual dosage is 10 mg once daily. In patients with reflux oesophagitis, the usual dosage is 20 mg once daily for 4 weeks' treatment; if this dosage is not sufficient, administration can be extended to 8 weeks. If maintenance treatment is required (reflux oesophagitis recurrence or recrudescence),

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Features and properties of vonoprazan

Alternative names	TAK 438; TAK-438; Takecab®; Vonoprazan fumarate
Class	Amines, Pyridines, Pyrroles, Small-molecules, Sulfonamides
Mechanism of action	Potassium-competitive acid blockers
Route of administration	Oral
Pharmacodynamics	Selectively and competitively inhibits gastric proton pump enzyme H^+, K^+-ATPase with a slow dissociation rate Stronger and longer-lasting effect than lansoprazole and SCH28080 in animal studies
Pharmacokinetics	Rapid absorption; accumulation in gastric tissue; limited CYP polymorphism
Most frequent adverse event	Nasopharyngitis
ATC codes	
WHO ATC code	A02B-X [other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)]
EphMRA ATC code	A2B9 (all other antiulcerants)
Chemical name	1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine monofumarate

the dosage is 10 mg once daily; if the efficacy is inadequate, the dosage can be increased to 20 mg once daily. Adjunct to *H. pylori* eradication, the usual dosage is vonoprazan 20 mg twice daily, administered concurrently with amoxicillin hydrate 750 mg twice daily, and clarithromycin 200 mg or metronidazole 250 mg twice daily, for 7 days.

Phase III development is underway for the prevention of recurrence of duodenal and gastric ulcer in patients on aspirin or NSAID therapy. Phase I development was conducted in the UK for gastro-oesophageal reflux; however, no further development has been reported [6].

1.1 Company Agreements

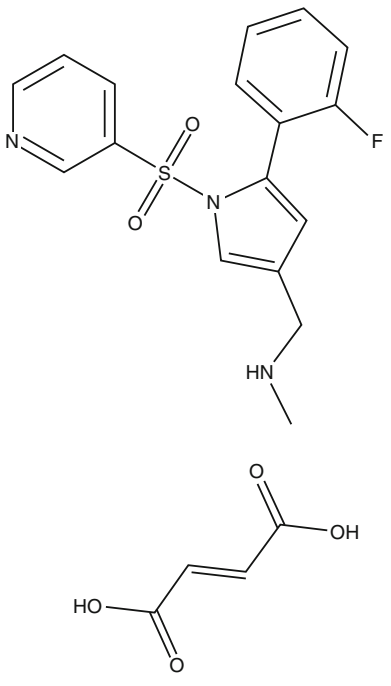
Takeda entered into an agreement with Otsuka Pharmaceutical in March 2014, for the co-promotion of vonoprazan in Japan [4, 7]. Under the terms of the agreement, Takeda will manufacture and market vonoprazan, and both the companies will jointly conduct informational activities for healthcare professionals [4]. Otsuka were to pay Takeda an upfront sum of JPY20 billion, and a milestone payment upon NDA approval [7]. Otsuka will be entitled to a percentage of sales revenues [4, 7].

2 Scientific Summary

2.1 Pharmacodynamics

In vitro studies using porcine microsomes determined that vonoprazan is highly selective and potassium competitive for binding to the gastric H^+, K^+-ATPase enzyme, with a K_i of 10 nmol/L at pH 7 [3] and a concentration required for 50 % inhibition (IC_{50}) of 17–19 nmol/L [3, 8]. The plateau of inhibition was reached within 200 s [3]. Binding was reversible [3, 8].

Vonoprazan has a slower dissociation rate than other P-CABs (with a dissociation half-life of 7.5 h in 20 mmol/L potassium chloride at pH 7) [3]. Ambient pH did not affect the inhibitory effects of vonoprazan; those of another P-CAB (SCH28080) and lansoprazole were weaker in less acidic environments; the IC_{50}s in pH 6.5 vs. pH 7.5 were 19 vs. 28, 140 vs. 2,500, and 7,600 vs. 66,000 nmol/L, for vonoprazan, SCH28080 and lansoprazole, respectively [8].



Chemical structure of vonoprazan

2.2 Pharmacokinetics

Absorption of vonoprazan is slowed if taken with food. The mean maximum concentration of vonoprazan following a single 20 mg dose was 24.3 and 26.8 ng/mL on an empty stomach and following a meal, respectively, and was reached after a median of 1.5 and 3.0 h, respectively [9]. The mean area under the concentration-time curve from time zero to 48 h was 222.1 and 238.3 ng·h/mL, respectively, and the mean elimination half-life was 7.7 h under both circumstances. Vonoprazan has a point-positive charge, allowing for a greater accumulation in parietal cells than that observed with previous P-CABs [3]. The drug showed limited CYP polymorphism [10].

2.3 Therapeutic Trials

2.3.1 Prevention of Recurrence of Duodenal and Gastric Ulcers

Twenty-four weeks' treatment with once daily vonoprazan 10 or 20 mg/day was shown to be noninferior to once daily lansoprazole 15 mg/day in a randomized, double-blind, multicentre, phase III trial that compared the agents for the secondary prevention of peptic ulcers associated with NSAID therapy [11]. The proportions of patients with recurrent duodenal or gastric ulcers at week 24 (primary endpoint) were 3.3 and 3.4 % in the vonoprazan 10 and 20 mg/day treatment groups, respectively, vs. 5.5 % in the lansoprazole group [differences of −2.2 (95 % CI −6.2 to 1.8) and −2.1 (95 % CI −6.1 to 2.0), respectively]; differences between the groups were not statistically significant. The recurrence rate at 12 weeks was 2.9, 3.0 and 5.0 %, respectively, and the incidence rate of haemorrhagic lesions at week 24 was 1.4, 1.0 and 2.0 %, respectively. The study involved 642 patients with a history of endoscopically confirmed peptic ulcers who required NSAID therapy.

In another similarly designed phase III trial, 24 weeks' treatment with once daily vonoprazan 10 or 20 mg/day was shown to be noninferior to once daily lansoprazole 15 mg/day for the secondary prevention of peptic ulcers associated with low-dose aspirin therapy [12]. At week 24, the recurrence rate of peptic ulcers (primary endpoint) was 0.5 and 1.5 vs. 2.8 % in recipients of vonoprazan 10 and 20 mg/day vs. lansoprazole 15 mg/day, respectively [differences of −2.3 (95 % CI −4.7 to 0.1) and −1.3 (95 % CI −4.1 to 1.5), respectively]; differences between the groups were not statistically significant. The recurrence rate at 12 weeks was 0.5, 0.5 and 0.9 %, respectively (not significant), and the incidence rate of haemorrhagic lesions at week 24 was 0.0, 0.0 and 2.9 %, respectively ($p < 0.05$ for both vonoprazan dosages vs. lansoprazole). The study involved 621 patients with a history of endoscopically confirmed peptic ulcers who required low-dose aspirin therapy.

2.3.2 Erosive Oesophagitis

The non-inferiority and superiority of once daily vonoprazan 20 mg/day to once daily lansoprazole 30 mg/day was demonstrated in a randomized, double-blind, multicentre, phase III study in patients with erosive oesophagitis; the proportion of healed patients at week 8 (primary endpoint) was 99.0 vs. 95.5 %, respectively [13]. The healing rate after 2 weeks' treatment was also superior with vonoprazan than with lansoprazole (90.7 vs. 81.9 %). Moreover, non-inferiority of 4 weeks' treatment with vonoprazan vs. 8 weeks' treatment with lansoprazole was demonstrated (healing rates of 96.6 vs. 95.5 %, respectively). In patients with LA Classification Grade C/D disease, the healing rates at 8 weeks were 98.7 vs. 87.5 %, respectively. A total of 409 patients with erosive oesophagitis were included in the study; patients were stratified by baseline grades of disease. An observation period of 3–7 days was followed by a treatment period of 8 weeks.

Results from a randomised, double-blind, multicentre, phase III trial comparing once daily vonoprazan (10 or 20 mg/day) with once daily lansoprazole 15 mg/day as a maintenance treatment for patients with healed erosive oesophagitis demonstrated that both dosages of vonoprazan were both noninferior and superior to lansoprazole, based on the proportion of patients with recurrence at week 24 (primary endpoint; 5.1 and 2.0 vs. 16.8 %, respectively) [14]. In patients with baseline LA Classification Grade C/D, the recurrence rates were 13.2 and 4.7 vs. 39.0 %, respectively. A total of 607 patients were included in the study. The 24-week maintenance treatment period followed a treatment period (for the initial erosive oesophagitis) of 2, 4 or 8 weeks (time spent in this period depended on time taken for endoscopic healing to occur).

Results from an earlier, randomized, double-blind, multicentre, phase II dose-ranging study ($n = 733$; vonoprazan 5, 10, 20 and 40 mg/day vs. lansoprazole 30 mg/day) indicated that all vonoprazan dosages were noninferior to lansoprazole, and a dosage of vonoprazan 20 mg/day was the recommended dosage for the treatment of erosive oesophagitis in phase III trials [15].

2.3.3 Helicobacter pylori Infections

The non-inferiority and superiority of vonoprazan to lansoprazole as a first-line triple therapy (with amoxicillin and clarithromycin) to eradicate *H. pylori* infection was

established in a randomised, double-blind phase III study [16]. Eradication (evaluated by the ^{13}C-urea breath test) was recorded in 92.6% of vonoprazan and 75.9 % of lansoprazole recipients (95 % CI of difference 11.2–22.1; $p < 0.0001$) [16]. In patients with clarithromycin resistance, the eradication rate was also significantly higher in vonoprazan than in lansoprazole recipients (82.0 vs. 40.0 %; $p < 0.0001$) [16]. A total of 650 *H. pylori*-positive patients with gastric or duodenal ulcer history were randomised to receive one of four 7-day courses as a first-line therapy: vonoprazan 20 mg twice daily or lansoprazole 30 mg twice daily plus clarithromycin 200 or 400 mg twice daily plus amoxicillin 750 mg twice daily [16]. In patients for whom first-line therapy failed and who received an additional 7-day, second-line course of vonoprazan 20 mg twice daily plus amoxicillin 750 mg twice daily plus metronidazole 250 mg twice daily, an eradication rate of 98 % was reported (49 of 50 patients) [17].

Key phase III clinical trials of vonoprazan in Japan (Takeda)

Drugs(s)	Indication	Status	Identifier
Vonoprazan vs. lansoprazole	Gastric ulcer	Completed	NCT01452711; TAK-438/CCT-101; U1111-1123-8551; JapicCTI-111612
Vonoprazan vs. lansoprazole	Duodenal ulcer	Completed	NCT01452724; TAK-438/CCT-102; U1111-1123-8648; JapicCTI-111608
Vonoprazan + aspirin vs. lansoprazole + aspirin	Prevention of recurrent gastric or duodenal ulcers	Completed	NCT01452763; TAK-438/CCT-302; U1111-1123-8746; JapicCTI-111610
Vonoprazan + aspirin vs. lansoprazole + aspirin	Prevention of recurrent gastric or duodenal ulcers (extension study)	Completed	NCT01456247; TAK-438/OCT-302; U1111-1123-9658; JapicCTI-111616
Vonoprazan + NSAID vs. lansoprazole + NSAID	Prevention of recurrent gastric or duodenal ulcers	Completed	NCT01452750; TAK-438/CCT-301; U1111-1123-8722; JapicCTI-111613
Vonoprazan + NSAID vs. lansoprazole + NSAID	Prevention of recurrent gastric or duodenal ulcers (extension study)	Completed	NCT01456260; TAK-438/OCT-301; U1111-1123-8762; JapicCTI-111611
Vonoprazan	Prevention of recurrent gastric or duodenal ulcers	Completed	NCT01568398; TAK-438/OCT-304; U1111-1128-6012; JapicCTI-121790
Vonoprazan	Prevention of recurrent gastric or duodenal ulcers	Completed	NCT01568385; TAK-438/OCT-303; U1111-1128-5905; JapicCTI-121789
Vonoprazan	Non-erosive gastroesophageal reflux disease	Completed	NCT01474369; TAK-438/CCT-201; U1111-1125-1115; JapicCTI-111663
Vonoprazan	Proton pump inhibitor-resistant erosive oesophagitis	Completed	NCT01630746; TAK-438/OCT-002; U1111-1130-9074; JapicCTI-121882
Vonoprazan vs. lansoprazole	Healed erosive oesophagitis	Completed	NCT01459367; TAK-438/CCT-003; U1111-1125-1054; JapicCTI-111662
Vonoprazan	Healed erosive oesophagitis	Completed	NCT01452776; TAK-438/OCT-001; U1111-1123-9677; JapicCTI-111615
Vonoprazan vs. lansoprazole	Erosive oesophagitis	Completed	NCT01452698; TAK-438/CCT-002; U1111-1123-8356; JapicCTI-111607
Vonoprazan + amoxicillin + clarithromycin vs. lansoprazole + amoxicillin + clarithromycin	*H. pylori* infections in patients with scarred gastric or duodenal ulcers	Completed	NCT01505127; TAK-438/CCT-401; U1111-1126-5073; JapicCTI-111722

2.4 Adverse Events

Vonoprazan was generally well tolerated in clinical trials [11–14, 16, 17].

During the 7-day treatment period in patients with *H. pylori* infections, the incidence of drug-related adverse events was 20.4 and 24.6 % in first-line recipients of the vonoprazan 20 mg twice daily- and lansoprazole 30 mg twice daily-based triple therapies [16, 17]; in second-line vonoprazan-based triple therapy, the incidence of drug-related adverse events was 16.0 % [17]. Most adverse events were of mild severity.

The incidence of adverse events during 8 weeks treatment of patients with erosive oesophagitis was 22.2 % with vonoprazan 20 mg/day and 22.3 % with lansoprazole 30 mg/day treatment; the most common was nasopharyngitis (3.4 vs. 4.0 %, respectively) [13].

In the three studies lasting 24 months, one for the prevention of erosive oesophagitis recurrence [14] and two for the prevention of peptic ulcers (in patients taking NSAIDs [11] or low-dose aspirin [12]), the overall incidence of adverse events was similar between treatment groups (54.0–71.6 and 58.8–75.7 vs. 51.2–76.7 % of vonoprazan 10 and 20 mg/day vs. lansoprazole 15 mg/day, respectively) [11, 12, 14], as were the incidence of serious adverse events and the incidence of adverse events leading to treatment discontinuation [11, 12].

3 Current Status

Vonoprazan received its first global approval on 26 December 2014 for the treatment of acid-related diseases in Japan [4].

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