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MONOGRAPH

AVATROMBOPAG MALEATE

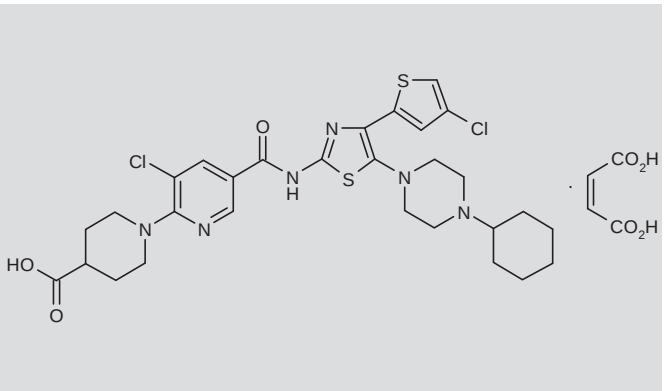
USAN

Thrombopoietin Receptor Agonist
Treatment of Thrombocytopenia

AKR-501
E-5501
YM-477

1-[3-Chloro-5-[*N*-[4-(4-chlorothien-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]carbamoyl]pyridin-2-yl]piperidine-4-carboxylic acid maleate

InChI: 1S/C29H34Cl2N6O3S2.C4H4O4/c30-20-15-23(41-17-20)24-27(37-12-10-35(11-13-37)21-4-2-1-3-5-21)42-29(33-24)34-26(38)19-14-22(31)25(32-16-19)36-8-6-18(7-9-36)28(39)40;5-3(6)1-2-4(7)8/h14-18,21H,1-13H2,(H,39,40)(H,33,34,38);1-2H,(H,5,6)(H,7,8)/b;2-1-



$C_{33}H_{38}Cl_2N_6O_7S_2$
Mol wt: 765.727
CAS: 677007-74-8
CAS: 570406-98-3 (free base)
EN: 345673

SUMMARY

Avatrombopag maleate (E-5501) is a novel, orally active thrombopoietin receptor (TPO-R) agonist that mimics the biological effects of TPO. In preclinical studies, avatrombopag maleate stimulated megakaryocyte colony growth in a dose-dependent fashion, with maximum activity similar to that of TPO. A synergistic effect between avatrombopag maleate and TPO was also observed. Avatrombopag maleate induced platelet production in normal subjects in a dose-related manner. The drug was well tolerated at doses required to induce platelet production in normal individuals. The efficacy and safety of avatrombopag maleate have been investigated in patients with chronic immune thrombocytopenia (ITP) who had received at least one prior treatment for ITP. In a dose-finding study there were statistically more platelet responses at day 28 with avatrombopag maleate 20 mg/day than for placebo or avatrombopag maleate 2.5 mg/day. A 6-month extension study showed that the drug is able to support prolonged platelet responses. In these studies, avatrombopag maleate was in general well tolerated. Further development of avatrombopag maleate as a potential new treatment for thrombocytopenia is warranted.

Key words: Primary immune thrombocytopenia – Thombopoietin – Avatrombopag – E-5501 – AKR-501

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*Synthesis prepared by C. Estivill, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

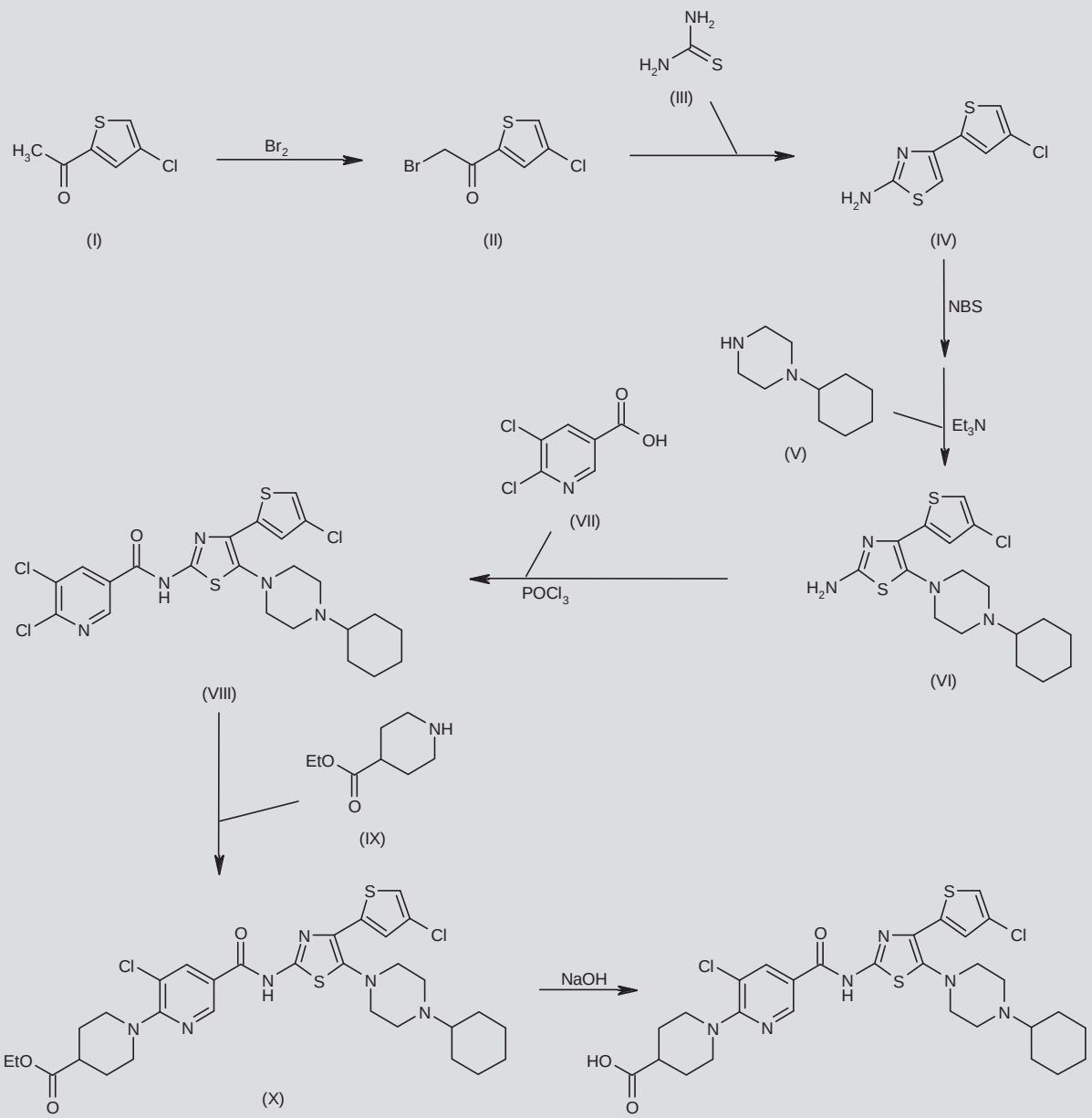
SYNTHESIS*

Bromination of 1-(4-chloro-2-thienyl)ethanone (I) with Br_2 in Et_2O gives 2-bromo-1-(4-chloro-2-thienyl)ethanone (II), which by cyclocondensation with thiourea (III) in EtOH at 80 °C provides 2-amino-4-(4-chloro-2-thienyl)thiazole (IV). Treatment of thiazole (IV) with NBS in DMF and subsequent condensation with 1-cyclohexylpiperazine (V) by means of Et_3N at 70 °C affords the 5-piperazinyl-thiazole derivative (VI). Coupling of the 2-aminothiazole (VI) with 5,6-dichloronicotinic acid (VII) in the presence of $POCl_3$ in pyridine yields amide (VIII), which is then condensed with ethyl isonipecotate (IX) in THF at 50 °C to obtain the ethyl 1-(pyridyl)piperidine-4-carboxylate derivative (X). Finally, ethyl ester (X) is hydrolyzed by means of NaOH in MeOH (1). Scheme 1.

BACKGROUND

Low platelet counts are a common hematological finding and may result from abnormal mechanisms of platelet production, distribution or destruction. A number of diverse etiologies are associated with thrombocytopenia, including chronic liver disease, infections, autoimmune diseases, drug-induced myelosuppression and primary hematological disorders such as leukemia or aplastic anemia. The clinical consequences of thrombocytopenia are an increased risk of

Scheme 1. Synthesis of Avatrombopag



bleeding, which is not easily predictable. However, a relationship does exist between the degree of thrombocytopenia and the frequency and severity of bleeding episodes (2).

With the exception of immune-mediated thrombocytopenia, where corticosteroids and intravenous immunoglobulins consistently increase the platelet count in the majority of patients (3), treatment for severe thrombocytopenia has been limited to transfusion therapy. Despite their efficacy and rapidity of action, platelet transfusions have several limitations. The major drawbacks are the transiency of their effect, a significant percentage of transfusion reactions and the development of inadequate platelet response due to human leukocyte antigen (HLA) alloimmunization (4).

The discovery and cloning of human thrombopoietin (TPO) and its receptor (TPO-R) stimulated the development of agents with TPO-like activity that could effectively stimulate platelet production and improve or abrogate thrombocytopenia. The first-generation TPO-R agonists were recombinant human TPO and a nonglycosylated, truncated form of TPO called megakaryocyte growth and differentiation factor (MGDF). MGDF was chemically coupled to polyethylene glycol (PEG-MGDF) to increase the half-life of the molecule (5). Studies with both agents were discontinued after a few healthy volunteers developed an IgG_4 antibody to PEG-MGDF that cross-reacted and neutralized endogenous TPO, thereby resulting in severe thrombocytopenia (6).

In recent years, research has been directed at generating TPO-R agonists with no sequence homology to endogenous TPO. Two classes of these second-generation agents have been tested in clinical trials: peptide TPO-R agonists and nonpeptide TPO-R agonists. Agents that have completed phase III trials are romiplostim, a peptide TPO-R agonist, and eltrombopag, a nonpeptide TPO-R agonist (5).

The present review will focus on avatrombopag maleate, a novel nonpeptide TPO-R agonist. This compound was originally synthesized by Yamanouchi Pharmaceutical (Ibaraki, Japan) with the code name YM-477 (7). The molecule was later acquired by AkaRx (Paramus, New Jersey), which renamed it AKR-501 and commenced its clinical development. AkaRx is now a wholly-owned subsidiary of Eisai, Inc., which has the exclusive worldwide rights to develop, market and manufacture the compound, now known as E-5501.

PRECLINICAL PHARMACOLOGY

Avatrombopag binds specifically to the TPO-R. In fact, it supports the proliferation of TPO-R-expressing Ba/F3 cells in a concentration-dependent fashion, but has no effect on parental Ba/F3 cells not expressing the TPO-R. The compound demonstrated a half-maximal effective concentration (EC_{50}) value of 3.3 ± 0.2 nM in this assay, with the maximum proliferative activity equivalent to the maximum activity of recombinant human TPO (rhTPO) (8).

Likewise, avatrombopag promoted megakaryocyte colony formation from human cord blood $CD34^+$ cells with similar activity to rhTPO. There were no notable differences between the morphology of megakaryocyte colonies generated with the two agents. Furthermore, avatrombopag and rhTPO induced similar polyploidization of megakaryocytes from granulocyte colony-stimulating factor-mobilized peripheral blood $CD34^+$ cells in liquid culture (8). Avatrombopag does not compete with rhTPO for the TPO-R and the two agents actually show a synergistic effect in vitro (7).

Avatrombopag activates the TPO-R of human and chimpanzee blood platelets, but has no effect on platelets of olive baboons, cynomolgus monkeys, rhesus monkeys, common marmosets, squirrel monkeys, beagle dogs, guinea pigs, rabbits, rats and hamsters (8).

In analogy with what has been found with eltrombopag (9), another small-molecule TPO-R agonist, the species-specific activity of avatrombopag appears to depend on the presence of a histidine residue at position 499 in the transmembrane domain of the TPO-R. This residue is conserved between humans and chimpanzees, but is not found in other species. In support of this hypothesis, mouse TPO-R with a histidine 499 substitution was sufficient to support avatrombopag-stimulated growth of Ba/F3 cells (10). In summary, the available evidence suggests that avatrombopag exerts its biological effects through binding to the transmembrane domain of the TPO-R.

The in vivo pharmacological effects of avatrombopag on human platelet production were assessed using an NOD/SCID mouse model transplanted with human fetal liver $CD34^+$ cells (8). Doses of 0.3, 1 and 3 mg/kg/day of avatrombopag were orally administered once daily for 14 days to NOD/SCID mice that stably produced human platelets. There was a dose-dependent increase in the number of human platelets, with an approximately 2.7-fold increase at 1 mg/kg/day and a 3.0-fold increase at 3 mg/kg/day on day 14 after the start of administration. The minimum effective dose was 1 mg/kg/day. Once administration was discontinued, the human platelet count returned to nearly pretreatment levels. Because of the species specificity of avatrombopag, no significant changes in the murine platelet count were observed.

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics of avatrombopag maleate have been studied in a randomized phase I trial in healthy volunteers (11). The drug was well absorbed from the gastrointestinal tract and showed linear pharmacokinetics following single and multiple doses. There was no significant food effect or drug–drug interaction. The serum half-life of the compound was approximately 16 hours. The mean observed maximum concentration (C_{max}) following single doses increased from 5.67 ng/mL at 1 mg to 388 ng/mL at 100 mg. The mean observed area under the curve (AUC) increased from 174 ng*h/mL at 1 mg to 11,052 ng*h/mL at 100 mg.

CLINICAL STUDIES

The safety, pharmacokinetics and pharmacodynamic activity of avatrombopag maleate (increase in platelet count) were assessed in a randomized phase I study in healthy volunteers (11). The drug was given as single and multiple oral doses. In the single-dose study, 63 subjects (7 dose cohorts of 9 subjects each) were randomized in a 2:1 ratio to receive increasing doses of avatrombopag maleate (1, 3, 10, 20, 50, 75 and 100 mg) or placebo. In the multiple-dose study, 45 subjects (5 dose cohorts of 9 subjects each) were randomized 2:1 to receive increasing doses of avatrombopag maleate (3, 10, 20, 50 and 100 mg) or placebo daily for 14 days. No serious drug-related adverse events were reported at any dose both in the single- and multiple-dose study with doses up to 20 mg/day given for 10-14 days (12). There was a highly significant dose- and concentration-related effect on platelet count. A > 50% increase over the baseline platelet count, the predefined protocol endpoint, was achieved in five of six volunteers given a dose of 100 mg. In the multiple-dose study, all 6 volunteers given daily doses of 10 mg for 14 days had a > 50% increase in the platelet count. Safety data for these patients were reviewed by the Food and Drug Administration (FDA), which approved escalation to the 20 mg/day cohort with a revised pharmacodynamic limit of five subjects with a platelet count > 500 × 10^9/L. This target was achieved by day 10 in all six of the volunteers receiving 20 mg/day and the study was therefore stopped.

The effects of avatrombopag maleate in patients with ITP were initially investigated in a double-blind, randomized phase II trial (501-

CL-003) (13, 14). This was a dose-finding study of 4 weeks' duration comparing different doses of avatrombopag maleate (2.5, 5.0, 10.0 and 20.0 mg/day) versus placebo in different cohorts of adult patients with chronic/relapsed ITP who had received at least one prior ITP therapy. Subjects 18 years of age or older were enrolled if they had a baseline platelet count of < 30 x 10^9/L or < 50 x 10^9/L and were on stable corticosteroid therapy. Exclusion criteria included splenectomy within 4 weeks prior to study treatment and a history of cardiovascular or thromboembolic disease. Platelet counts and safety evaluations were performed weekly. The primary endpoint was the response rate at day 28, wherein response was considered to achieve a platelet count ≥ 50 x 10^9/L and a rise of ≥ 20 x 10^9/L from baseline. A total of 64 patients were randomized to avatrombopag maleate (2.5, 5, 10 or 20 mg) or placebo in a 3:3:3:3:1 randomization ratio, respectively. Results showed a dose-dependent response rate at day 28 (Table I). There were more responses with avatrombopag maleate 20 mg than with placebo (80% vs. 0%; *P* = 0.0036) or avatrombopag maleate 2.5 mg (80% vs. 13.3%; *P* = 0.0007). In the combined avatrombopag maleate group, the response rate was 51.2% in non-splenectomized patients and 44.4% in splenectomized patients; in the 20-mg group, the response rate was 88.9% in non-splenectomized patients and 66.7% in splenectomized patients. In the 20-mg dose arm, 93.3% of patients responded by day 7. Peak platelet counts were observed on day 14 in both the 10- and 20-mg arms. Platelet count reductions were observed in the 20-mg arm after day 14, which may at least partly be explained by dose interruptions/discontinuations due to the high platelet counts. In fact, two subjects in the 20-mg arm withdrew due to high platelet counts (≥ 500 x 10^9/L).

Avatrombopag maleate was generally well tolerated. There were no clinically relevant changes in vital signs or physical examination findings. Treatment-emergent adverse events (TEAEs) were observed with a similar frequency across all dose groups. Most of these adverse events were mild and transient. TEAEs occurring in ≥ 10% of avatrombopag maleate-treated patients included fatigue (20.3%), headache (20.3%) and epistaxis (15.3%). TEAEs were not reported in the five subjects in the placebo group. Three subjects (two in the 2.5-mg and one in the 10-mg avatrombopag maleate group) reported serious TEAEs: in the 2.5-mg group, one patient reported thrombocytopenia and one a gastrointestinal (GI) bleed; in the 10-mg group, one patient with a significant history of cardiovascular disease suffered from multiple thrombotic episodes, a transient ischemic attack and a myocardial infarction on day 20, as well as retinal artery occlusion 14 days after avatrombopag maleate was discontinued. At the time of the events his platelet counts were between 40 and 50 x 10^9/L. Three other patients discontinued avatrombopag maleate due to adverse events; one patient experienced grade 2 musculoskeletal chest pain and, as previously mentioned, two patients had a grade 3 increase in platelet count with no clinical consequences.

A 6-month extension study, 501-CL-004, evaluated the long-term efficacy, safety and tolerability of avatrombopag maleate in the 53 patients who completed the previous phase II study (15, 16). Responders in 501-CL-003 continued to receive their original blinded dose, whereas non-responders initially received open-label avatrombopag maleate 10 mg once daily. The dose was increased by 10 mg every 14 days, depending on subject response (to a maximum of 40 mg once daily for non-responders and blinded dose plus 20 mg once daily for responders). Efficacy analyses included only the 53 subjects in 501-CL-004, whereas safety analyses were performed on combined data from both 501-CL-003 and 501-CL-004 (N = 64). The primary efficacy endpoint was the proportion of patients who in the absence of rescue medication achieved a durable platelet response. This was defined as a platelet count ≥ 50 x 10^9/L, with an increment of at least 20 x 10^9/L from baseline for 75% of the time over the last 14 weeks of the treatment period. A durable platelet response was achieved in 52.8% of all patients. The response rate was 35.7% among previous non-responders in the CL-003 study and 72% among previous responders. The platelet response rate ranged from 61% to 77% at on-therapy visits, and was consistently higher in previous responders than previous non-responders at all assessment time points during the study. Median platelet counts were maintained for the duration of treatment. The effectiveness of avatrombopag maleate was also shown by the reduction of concomitant ITP medications. Among patients taking steroids, 54.2% decreased their use by > 50%, including 33.3% who discontinued their use permanently. The severity of bleeding events was graded according to the World Health Organization (WHO) scale: grade 1, petechial bleeding; grade 2, mild blood loss; grade 3, gross blood loss; and grade 4, debilitating blood loss (17). Bleeding occurred in 43 of the 64 patients (67.2%); 3 had a clinically significant grade 3 bleed (epistaxis, hemorrhagic diathesis or intracranial bleed) and 1 had a grade 4 GI bleed related to hemorrhagic gastritis. All other bleeding events were grade 1 or 2.

TEAEs were experienced by all 64 patients, but were mostly mild, transient and resolved completely. Nevertheless, 10 of 64 (16%) patients discontinued treatment because of adverse events. The most common TEAEs were fatigue (37.5%), headache (32.8%), epistaxis (25.0%) and confusion (20.3%). Serious TEAEs were reported in 12 of 64 (18.8%) patients. Nine patients (14%) met the criteria for rebound worsening of thrombocytopenia, defined as a platelet count that decreased to < 10 x 10^9/L upon discontinuation of the drug. Thromboembolic events were reported in 4 of 64 (6.3%) subjects

Table I. *Response to treatment with avatrombopag maleate in study 501-CL-003.*

	2.5 mg (n = 15)	5 mg (n = 15)	10 mg (n = 14)	20 mg (n = 15)	Placebo (n = 5)
Responders on day 28, number (%)	2 (13)	8 (53)	7 (50)	12 (80)	0
P value vs. placebo*	NS	NS	NS	0.0036	

*Fisher's exact test; NS, not significant.

(deep vein thrombosis, stroke, myocardial infarction, retinal artery occlusion), 3 of whom had multiple risk factors for thrombosis. The fourth subject had grade 1 superficial thrombophlebitis.

CONCLUSION

Several agents that stimulate the TPO receptor have been developed for the treatment of thrombocytopenia. Two of these, romiplostim and eltrombopag, have already been licensed for use in ITP. ITP is actually a good model to explore the efficacy of new TPO-R agonists, since it is characterized by impaired platelet production and a relative TPO deficiency (3).

Both in the 4-week dose-finding study and in the 6-month extension study in patients with chronic, relapsed/refractory ITP, avatrombopag maleate appeared to have an excellent activity and safety profile. In general, the drug was well tolerated. However, grade 3/4 thrombotic arterial events were seen in four patients who already had multiple significant risk factors.

The development of avatrombopag maleate for ITP is advancing into a difficult and competitive environment. The oral administration of avatrombopag maleate might give it an edge over romiplostim, which is administered subcutaneously. It may also potentially be more convenient than the other oral agent, eltrombopag, in that it can be taken without concern for food interactions and has no discernible hepatotoxicity. Such characteristics provide a rationale for the continued development of avatrombopag maleate in ITP.

Nevertheless, it is still too premature to anticipate the role and the position of avatrombopag maleate in the treatment algorithm of patients with thrombocytopenia. In order to grant marketing approval in adults with chronic ITP, the FDA has requested a head-to-head comparison with eltrombopag in a randomized, double-blind, 26-week phase III trial with an open-label 2-year extension (ClinicalTrials.gov Identifier: NCT01433978). Another randomized, double-blind, 26-week phase III trial with an open-label extension phase will be conducted in Europe to evaluate the efficacy and safety of oral avatrombopag maleate plus standard of care versus placebo (ClinicalTrials.gov Identifier: NCT01438840).

What about other conditions characterized by thrombocytopenia? At present, avatrombopag maleate has been investigated only in chronic hepatitis C virus-related thrombocytopenia requiring antiviral treatment (ClinicalTrials.gov Identifier: NCT01355289). Another trial in subjects with chronic liver diseases and thrombocytopenia prior to elective surgical or diagnostic procedures has been completed (ClinicalTrials.gov Identifier: NCT00914927), but results have not yet been reported.

Like other TPO-R agonists, there are a number of potential complications associated with the long-term use of avatrombopag maleate. There is a concern for an increased number of thromboembolic events, and four cases (6.3%) have already been reported during the phase II studies. These findings suggest that in patients who are at high risk of thrombotic events, the use of TPO-R agonists should be carefully pondered.

Rebound thrombocytopenia has been consistently reported with all TPO-R agonists and in 14% of patients in the phase II extension study of avatrombopag maleate. It is a potentially dangerous event, as patients may be at risk of life-threatening bleeding. In this context, it is appropriate to remark that TPO-R agonists such as avatrombopag maleate are growth factors, the action of which is limited to the time of administration. In conditions such as chronic ITP, prolonged treatment of indefinite duration is required and discontinuation of these agents is not contemplated unless there is clinical evidence of disease remission.

Finally, reversible bone marrow fibrosis has been described with the use of both romiplostim and eltrombopag, and ongoing studies will clarify whether this is a significant risk with this class of agents.

In conclusion, avatrombopag maleate is a promising new orally available TPO-R agonist currently undergoing phase III trials in ITP. The results of these studies will help determine the optimal place for this agent in our therapeutic armamentarium.

SOURCE

Eisai Co., Ltd. (JP).

DISCLOSURES

The author has been a consultant for Amgen, GlaxoSmithKline, Suppremol, Symphogen and Nycomed, and has received honoraria for speaking at medical conferences from Amgen and GlaxoSmithKline.

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