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Review

Tenecteplase FDA approval in 2025 for Acute Ischaemic Stroke: Pharmacology & Molecular Advantages

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ABSTRACT

Background: Acute ischaemic stroke (AIS) is the predominant subtype of stroke responsible for significant global morbidity and mortality. Early restoration of cerebral perfusion via thrombolysis within a defined therapeutic window is critical to minimize irreversible neuronal injury. Traditionally, alteplase, a recombinant tissue plasminogen activator (rt-PA), has been the only FDA-approved thrombolytic for AIS for nearly three decades. However, limitations including short half-life and complex infusion regimens have driven interest in alternative agents. Tenecteplase (TNK) is a genetically modified tPA variant with enhanced pharmacokinetic properties that has emerged as an attractive candidate. Original FDA approval of tenecteplase was for ST-elevation myocardial infarction; in March 2025 the U.S. FDA extended approval to AIS in adults, recognizing evidence of non-inferior efficacy and comparable safety versus alteplase in randomized trials and meta-analyses.

Clinical Benefits: Tenecteplase offers several practical and clinical advantages over alteplase, including single-bolus administration, longer plasma half-life, and enhanced fibrin specificity, which can improve early reperfusion and streamline acute stroke workflows. Evidence from updated meta-analyses demonstrates similar or superior functional outcomes, recanalization rates, and neurologic recovery, with safety profiles comparable to alteplase.

Pharmacology & Molecular Advantage: Molecular modifications in tenecteplase confer greater resistance to plasminogen activator inhibitor-1 (PAI-1) and prolonged activity at clot sites, enabling simplified dosing without infusion pumps.

Conclusion: The 2025 FDA approval of tenecteplase for AIS represents a significant advancement in stroke therapeutics, aligning molecular innovations with clinical efficiency to improve real-world care.

This review synthesizes the pharmacological properties, molecular advantages, and clinical trial evidence that culminated in this regulatory milestone, while examining the implications for acute stroke management and future research directions.

Keywords: Tenecteplase, Acute Ischaemic Stroke, Pharmacology

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INTRODUCTION

Acute ischemic stroke remains a leading cause of mortality and long-term disability worldwide, with thrombolytic therapy representing a cornerstone of acute management for eligible patients. For nearly two decades, alteplase (recombinant tissue plasminogen activator, rt-PA) has been the only FDA-approved thrombolytic agent for AIS, establishing the standard of care for patients presenting within 4.5 hours of symptom onset.[1,2] Despite its proven efficacy, alteplase's requirement for bolus administration

followed by a 60-minute continuous infusion, coupled with its relatively short half-life and susceptibility to inhibition by endogenous plasminogen activator inhibitor-1 (PAI-1), has prompted the search for more pharmacologically optimized alternatives.[2,3]

Tenecteplase (TNK-tPA), a genetically engineered variant of alteplase developed through targeted amino acid substitutions, emerged as a promising candidate with superior pharmacokinetic and pharmacodynamic properties.[4,5] Initially approved for acute myocardial infarction over a decade ago, tenecteplase demonstrated comparable efficacy to alteplase with the added benefit of single-bolus administration.[6,7] The accumulation of robust clinical evidence from multiple randomized controlled trials and meta-analyses comparing tenecteplase to alteplase in AIS patients ultimately led to FDA approval in early March 2025.[1] This regulatory milestone represents a paradigm shift in stroke thrombolysis, offering clinicians a more practical and potentially more effective therapeutic option.[1,8]

Pharmacological Properties of Tenecteplase

Tenecteplase is a third-generation fibrinolytic agent created through bioengineering modifications to the wild-type tissue plasminogen activator molecule.[9,10] The development of tenecteplase involved the strategic exchange of six amino acids at three distinct sites within the alteplase structure, each modification conferring specific pharmacological advantages.[7,11] These molecular alterations fundamentally transformed the drug's pharmacokinetic profile while preserving its thrombolytic efficacy.

The first critical modification involves an asparagine-to-threonine substitution at position 103 within the first kringle domain (K1), which substantially prolongs the plasma half-life of tenecteplase.[6,12] This structural change reduces hepatic clearance, extending the half-life to approximately 20-24 minutes compared to alteplase's 4-5 minutes—a six-fold increase that enables single-bolus administration.[5,13] The second modification consists of a tetra-alanine substitution at positions 296-299 in the protease domain, which dramatically enhances fibrin specificity and confers resistance to PAI-1 inhibition.[6,14] The third alteration involves modifications that collectively optimize the molecule's interaction with fibrin-bound plasminogen while minimizing systemic plasminogen activation.[11,15]

In vitro studies have demonstrated that tenecteplase retains approximately 85% of the thrombolytic potency of wild-type rt-PA, while exhibiting markedly improved selectivity for fibrin-rich thrombi.[6] This enhanced fibrin specificity translates to more targeted clot lysis with reduced systemic fibrinogenolysis, potentially lowering the risk of hemorrhagic complications.[8,16] The pharmacological profile of tenecteplase thus represents a rational optimization of thrombolytic therapy, addressing key limitations of first-generation agents while maintaining therapeutic efficacy.[17,18]

Molecular Advantages over Alteplase

The molecular advantages of tenecteplase over alteplase are quantitatively substantial and clinically meaningful. Tenecteplase exhibits 14- to 15-fold higher fibrin specificity compared to alteplase, enabling preferential activation of plasminogen at the thrombus site while minimizing systemic effects.[5,15,19] This enhanced fibrin selectivity results from the tetra-alanine substitution at position 296, which increases the affinity of the molecule for fibrin-bound plasminogen while reducing its interaction with circulating plasminogen.[6,8] Consequently, tenecteplase produces less systemic depletion of circulating fibrinogen and α2-antiplasmin, potentially reducing bleeding complications.[8,20]

The prolonged half-life of tenecteplase—six times longer than alteplase—represents a transformative pharmacokinetic advantage.[5,13] This extended circulation time permits single-bolus administration over 5-10 seconds, eliminating the need for continuous infusion and associated infusion pumps.[2,14] The

practical implications are substantial: simplified administration reduces medication preparation time, minimizes dosing errors, and facilitates more rapid treatment initiation in time-critical stroke care.[1,21] Additionally, the bolus administration format is particularly advantageous in pre-hospital settings and during inter-facility transfers, where maintaining continuous infusions presents logistical challenges.[22]

Perhaps most clinically significant is tenecteplase's 80-fold increased resistance to inactivation by PAI-1 compared to alteplase.[5,6] PAI-1 is the primary physiological inhibitor of tissue plasminogen activator, and its plasma concentrations vary considerably among individuals based on genetic factors, metabolic conditions, and acute-phase responses.[23] Patients with elevated PAI-1 levels—common in diabetes, obesity, and acute inflammatory states—may exhibit reduced responsiveness to alteplase.[24]

Tenecteplase's marked resistance to PAI-1 inhibition theoretically provides more consistent thrombolytic activity across diverse patient populations, potentially improving recanalization rates in patients with high endogenous PAI-1 levels.[6,14] These molecular advantages collectively position tenecteplase as a pharmacologically superior alternative to alteplase, with the potential to deliver enhanced clinical outcomes.[9,25]

Clinical Trials and Evidence Leading to the 2025 Approval

The path to FDA approval was paved by an extensive body of clinical evidence from multiple phase II and phase III randomized controlled trials, complemented by numerous systematic reviews and meta-analyses. Early dose-finding studies established the safety profile of tenecteplase in AIS patients, with initial investigations exploring doses ranging from 0.1 to 0.5 mg/kg.[6] A pivotal NINDS-funded pilot study was halted at the 0.5 mg/kg dose due to symptomatic intracranial hemorrhages, leading to a subsequent focus on lower doses.[6] A landmark phase IIB trial by Parsons et al. demonstrated that tenecteplase 0.25 mg/kg achieved significantly better reperfusion and clinical improvement at 24 hours compared to alteplase, with 72% of patients in the higher-dose tenecteplase group achieving absence of serious disability at 90 days versus 40% with alteplase (P=0.02), without increased intracranial bleeding.[20]

The Norwegian Tenecteplase Stroke Trial (NOR-TEST), a multi-center randomized controlled trial, compared tenecteplase 0.4 mg/kg to standard alteplase, with the primary endpoint of a favorable functional outcome (modified Rankin Scale 0-1) at 90 days.[4] While NOR-TEST demonstrated non-inferiority, subsequent trials refined dosing strategies. The EXTEND-IA TNK trial series provided crucial evidence for large vessel occlusion (LVO) patients, with EXTEND-IA TNK Part 1 showing that tenecteplase 0.25 mg/kg improved reperfusion and 90-day functional outcomes compared to alteplase.[5,18] However, NOR-TEST 2 Part A was terminated early due to high symptomatic intracranial hemorrhage rates with the 0.4 mg/kg dose, reinforcing the safety profile of the 0.25 mg/kg dose.[5]

Multiple systematic reviews and meta-analyses have synthesized this evidence base. A comprehensive meta-analysis by Salamatullah et al. including ten randomized controlled trials with 5,123 patients, found no significant difference between tenecteplase and alteplase in modified Rankin Scale 0-1 outcomes (RR=1.04, 95% CI [0.99-1.10]) or symptomatic intracranial hemorrhage rates (RR=1.18, 95% CI [0.84-1.65]).[29] Critically, tenecteplase was associated with significantly higher complete recanalization rates (RR=1.17, 95% CI [1.00-1.36], P=0.05), and for LVO patients specifically, tenecteplase demonstrated significant improvement in excellent functional outcomes (RR=1.28, 95% CI [1.07-1.52], P=0.006).[29] Similarly, Oliveira et al.'s meta-analysis of eight studies encompassing 2,031 patients demonstrated that tenecteplase achieved higher recanalization rates (absolute risk difference=0.11) and early neurological improvement (absolute risk difference=0.10) compared to alteplase, with no significant differences in hemorrhagic complications or mortality.[17]

Additional trials, including ATTEST, TAAIS, and TNK-S2B, further corroborated tenecteplase's non-inferiority profile.[16] A systematic review by Kobeissi et al. analyzing nine randomized controlled trials confirmed comparable rates of mRS 0-1 and mRS 0-2 at 90 days, mortality, and symptomatic intracranial hemorrhage between treatments, while highlighting tenecteplase's superiority in LVO populations.[18] The cumulative evidence from these trials established that tenecteplase at 0.25 mg/kg is at least non-inferior to alteplase for general AIS populations and potentially superior for patients with large vessel occlusions, with a comparable safety profile.[2,9,19] This robust evidence base, demonstrating consistent safety and efficacy across diverse patient populations and clinical settings, provided the foundation for FDA approval in 2025.[1]

Implications for Acute Stroke Management

The FDA approval of tenecteplase carries profound implications for acute stroke care delivery, workflow optimization, and patient outcomes. The transition from alteplase to tenecteplase addresses several operational barriers that have historically complicated thrombolytic administration in emergency settings.[1] Single-bolus administration eliminates the need for infusion pumps, reduces medication preparation time, and minimizes the risk of dosing errors associated with weight-based continuous infusions.[5,21] These practical advantages translate to faster door-to-needle times, a critical quality metric in stroke care where every minute of delay results in measurable neurological deterioration.[22]

The simplified administration protocol is particularly advantageous in resource-limited settings, community hospitals, and pre-hospital environments where tenecteplase can be administered more readily than alteplase.[1,8] This accessibility may expand the reach of thrombolytic therapy to underserved populations and facilitate "drip-and-ship" protocols for patients requiring transfer to comprehensive stroke centers for endovascular therapy.[28] Furthermore, the lower cost of tenecteplase compared to alteplase presents significant economic advantages for healthcare systems, potentially improving the cost-effectiveness of stroke thrombolysis programs.[1,2]

From a clinical outcomes perspective, the evidence suggesting superior efficacy of tenecteplase in LVO patients has important implications for treatment algorithms.[18,29] Patients with large vessel occlusions represent a high-risk subgroup with substantial potential for disability, and the enhanced recanalization rates observed with tenecteplase may translate to improved functional outcomes in this population.[9,25] The comparable safety profile, with no increased risk of symptomatic intracranial hemorrhage at the 0.25 mg/kg dose, provides reassurance regarding the risk-benefit ratio of this transition.[17,29]

However, the implementation of tenecteplase requires careful attention to stakeholder engagement, formulary approval processes, and comprehensive training of clinical teams.[1] Early adopter experiences, such as that documented by Geisinger Health System, demonstrate that successful transitions require deliberate change management strategies, multidisciplinary collaboration, and robust quality monitoring systems.[1] As healthcare systems navigate this transition, ongoing surveillance of real-world outcomes will be essential to confirm the benefits observed in clinical trials and identify any population-specific considerations.[19,26]

Conclusion and Future Directions

The FDA approval of tenecteplase for acute ischemic stroke in 2025 represents a significant advancement in stroke therapeutics, culminating decades of research into optimized thrombolytic agents. Tenecteplase's superior pharmacological properties—including 15-fold higher fibrin specificity, six-fold longer half-life, and 80-fold greater PAI-1 resistance compared to alteplase—provide a strong mechanistic rationale for its clinical benefits.[5,6] The extensive clinical trial evidence demonstrating non-

inferiority in general AIS populations and potential superiority in large vessel occlusion patients, coupled with a comparable safety profile, has established tenecteplase as a viable and potentially preferred alternative to alteplase.[2,18,29]

Looking forward, several research priorities emerge. First, ongoing phase III trials will continue to refine optimal dosing strategies and identify patient subgroups most likely to benefit from tenecteplase.[9,30] Second, investigation of tenecteplase in extended time windows, wake-up stroke populations, and patients with contraindications to current thrombolytic protocols may expand treatment eligibility.[9,19] Third, the role of tenecteplase in combination with novel neuroprotective agents and advanced endovascular techniques warrants systematic evaluation.[12] Fourth, real-world effectiveness studies and implementation science research will be crucial to optimize the translation of clinical trial evidence into routine practice.[1,26]

Additional areas for future investigation include the potential application of tenecteplase for intra-arterial thrombolysis, central retinal artery occlusion, and use in patients on novel anticoagulants such as dabigatran.[19] The development of next-generation thrombolytics, building upon the tenecteplase platform, may further enhance efficacy and safety profiles.[1] Ultimately, the approval of tenecteplase not only provides clinicians with an improved therapeutic tool but also exemplifies the value of rational drug design and rigorous clinical evaluation in advancing stroke care. As healthcare systems worldwide adopt tenecteplase, continued vigilance through registry studies and post-marketing surveillance will ensure that the promise of this agent is fully realized in diverse clinical settings and patient populations.[25,27]

Abbreviations

AIS – Acute Ischemic Stroke, rt-PA – Recombinant Tissue Plasminogen Activator, TNK-tPA – Tenecteplase Tissue Plasminogen Activator, PAI-1 – Plasminogen Activator Inhibitor-1, K1 – Kringle Domain 1, α2-antiplasmin – Alpha-2 Antiplasmin, NINDS – National Institute of Neurological Disorders and Stroke, NOR-TEST – Norwegian Tenecteplase Stroke Trial, EXTEND-IA TNK – Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial Tenecteplase, ATTEST – Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis, TAAIS – Tenecteplase versus Alteplase for Acute Ischemic Stroke, TNK-S2B – Tenecteplase Stroke Trial Phase IIB, LVO – Large Vessel Occlusion, mRS – Modified Rankin Scale, RR – Relative Risk, CI – Confidence Interval, P – Probability Value, FDA – United States Food and Drug Administration.

Conflict of Interest

The authors declare no conflicts of interest relevant to this article.

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