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"Antidepressant Drug Etizolam"

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Abstract:
Antidepressants increased the risk compared to placebo of suicidal thinking and behaviour (suicidality) in children, adolescents, and young adults in short- term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SOLOPOSE-PLUS or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24 there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behaviour. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SOLOPOSE-PLUS is not approved for use in pediatric patients less than 12 years of age.

Keywords: *Antidepressants, Benzodiazepine, Etizolam, Disorder, Hypothermia, Insomnia, Relaxation, Inhibitions, Postsynaptic GABA, ETC.*

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I. Literature Of Review:

• **Paul I. Dargan and David M. Wood:** "Novel Psychoactive Substances: Classification, Pharmacology, and Toxicology".
• **Stephen Bazire:** "Psychotropic Drug Directory 2024".
• **WHO Expert Committee on Drug Dependence:** "Critical Review Report: Etizolam".

II. Introduction:

Etizolam is a thienodiazepine which is chemically related to benzodiazepine (BDZ) drug class; it differs from BDZs in having a benzene ring replaced with a thiophene ring. It isan agonist at GABA-A receptors and possesses amnesic, anxiolytic, anticonvulsant, hypnotic, sedative and skeletal muscle relaxant properties. Etizolam is a benzodiazepine that has anxiolytic, anticonvulsant, hypnotic, sedative, amnesic, and muscle-relaxant properties. It is used in adults with anxiety, depressive, somatization symptoms, generalized anxiety disorder, and panic disorder. The aim of the study was to chart review the use and safety of Etizolam in children and adolescents. This study was a retrospective chart Review. Patients who are on Etizolam and had at least 2 weeks follow-up were included for the study. The indications, effectiveness, and adverse effects were noted. Data was analysed using Epi Info 7. Descriptive statistics were used.

III. Structure Of Etizolam:

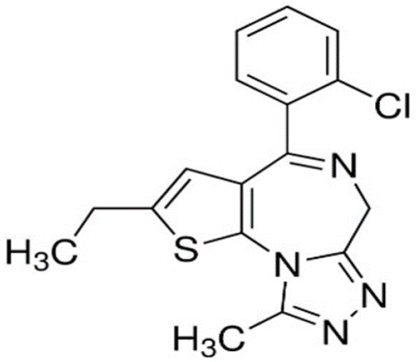

Figure 1: Chemical Structure Of Etizolam.

IV. Mechanism Of Action:

Etizolam is selectively a full agonist at GABA-A receptors to increase GABAergic transmission and enhance GABA-induced Cl- currents. It is reported to bind to the benzodiazepine binding site which is located across the interface between the alpha and gamma subunits. Benzodiazapines are reported to only bind to receptors that contain gamma 2 and alpha 1/2/3/5 subunits. Alpha-1-containing receptors mediate the sedative effects of Etizolam whereas alpha-2 and alpha-3 subunit-containing receptors mediate the anxiolytic effect. Etizolam shows high potency and affinity towards GABA-A receptor with alpha 1 beta 2 gamma 25 subunit combination. By binding to the regulatory site of the receptor, Etizolam potentiates GABA transmission by facilitating the opening of GABA-induced chloride channels. Etizolam is a specific antagonist at PAFR. It inhibits PAF-induced platelet aggregation by inhibiting PAF binding to the receptors located on the surface of platelets with an IC50 of 22nM.[22]

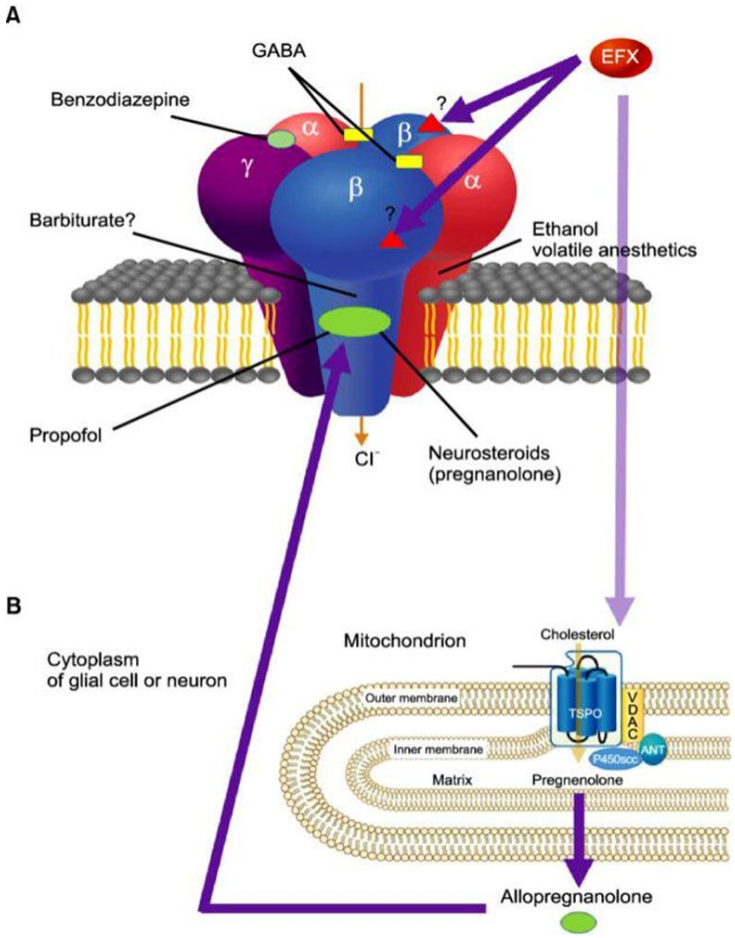

Figure:2. Schematic Action Mechanism Of Etifoxine (Efx).

V. Pharmacodynamics:

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). In vitro and in vivo studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Etaglamisa CNS depressant with anxiolytic, anticonvulsant, sedative-hypnotic muscle relaxant effects. Ir acts on the benzodiazepine site of the GABA-Alete tagonist to increase inhibitory GABAergic transmission throughouve hypnotic and muscleral Studies indicate that Etizolam mediates its pharmacological actionmo to 10 times more potency than that of diazepam. Clinical humanghout the central nervous systewed clinical effectiveness of Etizolam in relieving symptoms in patierele Generalized Anxiety Disorders with depressive symptoms. Etizolam als performed in Italy shoe-like neuropharmacological and behavioural effects, as well as minotuffins on cognitive functioning. It is shown to substitute the actions of a shon mediate sirinunate, pentobarbitol, in a drug discrimination study. Etizolam is a to inhibit PAR platelet-activating-factor (PAF) receptor and attenuates the recurrence of ching basubdural hematoma after neurosurgery in clinical studies. It is shown to inhibit PAF. Bronchoconstriction and hypotension.[12]

Table: 1. A Review Table With Composition (Film Coated Tablet):

CHEMICAL	MG VALUES
Etizolam IP	0.5mg
Escitalopram Oxalate IP	-
Equivalent to Escitalopram	10mg
Excipient	qs
Titanium Dioxide IP	qs

VI. Description (Escitalopram):

Orally administered selective serotonin reuptake inhibitor (SSRI), Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivatiye citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethyl-amino) propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate.

VII. Clinical Pharmacology:

Pharmacokinetics:

The single-and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours, With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy.[21]

Absorption And Distribution:

Etizolam is well absorbed from the intestines with a biological bioavailability of 93% following oral administration. After a single oral dosing of 0.5mg Etizolam, it takes approximately 0.9 hours to reach the peak plasma concentration of 8.3 ng/mL. a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food. The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable. The binding of escitalopram to human plasma proteins is approximately 56%.[9]

Metabolism And Elimination:

Oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Population Sub-Groups:

• **Age:** Escitalopram pharmacokinetics in subjects 2-65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and Cmax was unchanged. 10 mg is the recommended dose for elderly patients.

• **Gender:** In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, Cmax, and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

• **Reduced hepatic function:** Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients.

• **Reduced renal function:** In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance <20 mL/min). Drug-Drug Interactions In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4, -1A2, 2C9, -2C19, and -2E1. Based on in vitro data, escitalopram would be expected to have little inhibitory effect on in vivo metabolisın mediated by these cytochromes. While in vivo data to address this question are limited, results from drug interaction studies suggest that escitalopram, at a dose of 20 mg, has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect.[16]

VIII. Major Problems:

Patients with Major Depressive Disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders

themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behaviour (suicidality) in children, adolescents, and young adults (ages 18-24) with Major Depressive Disorder (MDD) and other psychiatric disorders. Short- tenn studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adulis beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

Volume Of Distribution:

Apparent distribution volume was 0.9±0.2 L/kg following a single oral dosing of 0.5mg Etizolam. Biotransformation of Etizolam is extensive and involves hydroxylation and conjugation. The main metabolite formed via 1'-hydroxylation is a-hydroxyEtizolam which retains pharmacological activity comparable to that of the parent drug, indicating that the action of metabolites may contribute to the clinical effects of Etizolam. CYP3A4 is predicted to be the main CYP enzyme responsible for mediating Etizolam metabolism. CYP2C18 and CYP2C19 are also involved in the metabolic pathways.[including Review]

Route Of Elimination:

In a rat study, the amounts of Etizolam excreted was 30% in urine and 70% in feces, while the values in a mouse study were 40% in urine and 60% in feces.

Half-Life:

The average elimination half-life of Etizolam following a single oral dose of 0.5mg is 3.4 hours but may be increased up to 17 hours depending on the rate of metabolism. The main metabolite a-hydroxyEtizolam displays a longer elimination half-life of 8.2 hours.

Adverse Effects:

Etizolam is reported to be "well tolerated with little side effects" when prescribed.

Physical Effects:

Decrease in energy, decreased heart rate, impaired coordination, sleepiness, respiratory depression, blurred vision, yawning, constricted pupils, decreased appetite, nausea and vomiting, muscle relaxation, dry mouth, headache, involuntary eye closure, rebound insomnia (prolonged use).[1]

Mental Effects:

Mood enhancement, relaxation, reduced anxiety, lowered inhibitions, sedative effects, mental confusion, short term memory loss.

Common Effects:

Some users report malaise after use but the majority of people who use on an occasional basis suggest there is little comedown or hangover. Using on a more frequent basis can lead to rebound anxiety and/or depression, with difficulty sleeping, problems falling asleep or waking early.[19]

Pharmacological Effects:

Etizolam (SOLOPOSE-PLUS) is a full benzodiazepine receptor agonist and so has a broadly similar pharmacological profile to benzodiazepine drugs such as diazepam. It has the full range of group-specific benzodiazepine effects: anxiolytic, sedative, hypnotic, anticonvulsant and muscle relaxant, and is approximately 10 times more potent than diazepam. It differs from drugs such as diazepam as it has selective and high affinity binding to postsynaptic GABA-A receptor alpha-2 subunit, which results in specific anxiolytic effects.

Tolerance, Dependence And Withdrawal:

Benzodiazepines such as Etizolam (SOLOPOSE-PLUS) which are more rapidly eliminated from the body are less likely to accumulate, and there is evidence to suggest that Etizolam is less likely. To induce tolerance and dependence compared with classical benzodiazepines. Hependence may develop with regular use of benzodiazepines, even in therapeutic doses for short periods. If benzodiazepines are discontinued abruptly after regular use, withdrawal symptoms may develop. Administration of regular doses of benzodiazepines can result in physical dependence, characterized by a withdrawal syndrome when the drug is discontinued. With larger doses, the physical dependence develops more rapidly.

Withdrawal Symptoms Include:

Anxiety, insomnia, headache, dizziness, tinnitus, anorexia, vomiting, nausea, tremor, weakness, perspiration, irritability, hypersensitivity to visual and auditory stimuli, palpitations, tachycardia (fast heart rate) and postural hypotension (drop in blood pressure on standing). In severe and rare cases of withdrawal from high doses, patienes may develop affective disorders or motor dysfunction: seizures, psychosis, agitation, confusion, and hallucinations. There is also evidence that links benzodiazepine use (in conjunction with alcohol) as a factor in offending.[23]

Long Term Effects/Known Harms:

Etizolam (SOLOPOSE-PLUS) is entirely metabolised by the liver and so is contraindicated in those with liver function issues. Loss of hypnotic effects and increased tolerance may be experienced with long term use. There is also a risk of dependence and addiction with repeated use. Benzodiazepines commonly cause drowsiness, ataxia (neurological conditions which affect balance and coordination), dysarthria (difficulty speaking), nystagmus (involuntary eye movement) and blepharospasm (involuntary closure of eyelids). Coma, hypotension (low blood pressure), bradycardia (slow heart beat) and respiratory depression occasionally occur but are seldom serious if these drugs are taken alone. Coma usually lasts only a few hours but may be prolonged in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis (breakdown of muscle tissue) and hypothermia. Co-ingestion of alcohol and other central nervous system depressants potentiates the effects of benzodiazepines and can increase toxicity.

Toxicity:

Major adverse effects include drowsiness, sedation, muscle weakness and incoordination, fainting, headache, confusion, depression, slurred speech, visual disturbances and changes in libido and tremor. Flumazenil is a competitive antagonist of GABA-A receptors and can be also used to reverse the effect of Etizolam (SOLOPOSE-PLUS) overdosage. Etizolam demonstrates no effects on fertility, development and teratogenicity. LD50 values of Etizolam when delivered orally, intraperitoneally, and subcutaneously are 3509mg/kg, 825mg/kg, and >5000mg/kg in rats, respectively, and 3070mg/kg, 783mg/kg and 5000mg/kg in mice, respectively.[28]

IX. Market Research:

SOLOPOSE-PLUS tablets is available in a blister of 10 tablets, such 4 blisters packed in a carton along with a package insert.

Etizolam (Solopose-Plus) Market Analysis:

Global Etizolam (SOLOPOSE-PLUS) Market Report 2024 Edition talks about crucial market insights with the help of segments and sub-segments analysis. In this section, we reveal an in-depth analysis of the key factors influencing Etizolam Industry growth. Etizolam market has been segmented with the help of its Type, Application , and others. Etizolam market analysis helps to understand key industry segments, and their global, regional, and country-level insights. Furthermore, this analysis also provides information pertaining to segments that are going to be most lucrative in the near future and their expected growth rate and future market opportunities. The report also provides detailed insights into factors responsible for the positive or negative growth of each industry segment.

Figure 3. Market Evaluation Of Etizolam

Application Segment Analysis Of Etizolam Market:

Chemical and materials are one of the most important industries for other sectors including automotive, pharmaceutical, personal care, consumer goods and others. The demand for high quality and environment friendly products is increasing in various end-use sectors. Thus, key manufacturers are focusing on technological advancement in production of high-quality chemicals. The segment analysis will help to understand which is the most attractive application/end use sector. It also provides the year on year (Y-O-Y) growth rate for each segment. Moreover, this study includes the detailed analysis of each segment to understand the key positive and negative factors which are impacting the growth of the Etizolam (SOLOPOSE-PLUS) Market.[EVALUATION DATA]

X. Results:

57 (38.51%) patients had been treated with Etizolam (SOLOPOSE-PLUS). The mean age of children was 13.59 years (7-18 years). Amongst the patients prescribed Etizolam, 37 (64.91%) had a data of follow-up of at least 2 weeks. 25 (67.57%) patients had moderate to complete improvement, 5 (13.51%) had mild improvement and 7 (18.92%) had no improvement. The adverse events were noted only in 3 (8.11%) patients.

XI. Discussion:

The current study is an initial observation of Etizolam (SOLOPOSE-PLUS) in children and adolescents. Etizolam was developed in 1978 [1]. The literature about its use and efficacy profile is Minimal even in adults, so it is not included in most of the guidelines for treatment of psychiatric symptoms and disorders. The available literature points to be helpful in reducing anxiety, depressive, and somatization symptoms. The animal studies have shown that Etizolam has a reduced liability to induce tolerance and dependence as against classical benzodiazepines [4]. However, there are a couple of reports of Etizolam dependence from India [11], Japan [12] and USA [13]. It is difficult to comment on Etizolam dependence in the current study because of the short follow-up period of only

XII. Conclusion:

Etizolam is effective in treating common Psychiatric symptoms in children and Adolescents and is well tolerated with minimal Adverse effects. Etizolam is effective in treating common psychiatric symptoms and disorders in children and adolescents and is well tolerated with minimal adverse effects. Indicated for the treatment of Generalized Anxiety Disorder with depression, panic disorder and insomnia.

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