Drug Development

Xanax

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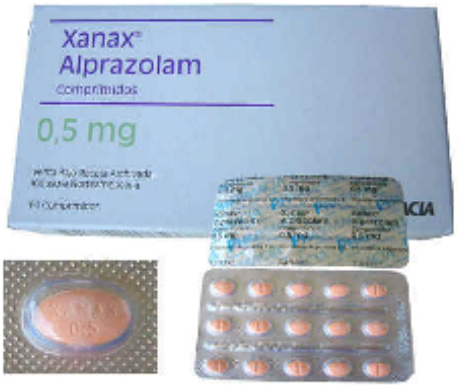
DESCRIPTION

Alprazolam is an analog of **1, 4 benzodiazepine class** of **central nervous system-active** compounds. It exists as white, crystalline powder at about 225°. It is soluble in organic solvents, but insoluble in water.



I. Lead Compound Discovery

Alprazolam was **first developed by Upjohn Laboratories of Kalamazoo**, Michigan in 1970s.

It is covered under U.S. Patent 3,987,052, which was filed on October 29, 1969. Then, it was granted on October 19, 1976, and expired in September 1993. Alprazolam is a derivative of an antidepressant similar to other earlier antidepressants such as Librium introduced in 1960. They both have a group called benzodiazepines. At that time, benzodiazepines were thought to be ineffective in treating panic disorder. It was perceived to be **rare** and **only treatable with tricyclic antidepressants**.

Upjohn first took the indication as panic disorder at the behest of a young psychiatrist, David Sheehan. From his clinical experience, Sheehan knew panic disorder is widespread among the populace and responsive to benzodiazepines. So, he suggested to market alprazolam specifically for anxiety disorders, which would cover a new diagnostic territory and emphasize the unique potency of the drug.

About 50 double blind studies were produced. It was proved that alprazolam is a **better and less toxic antidepressant** than its

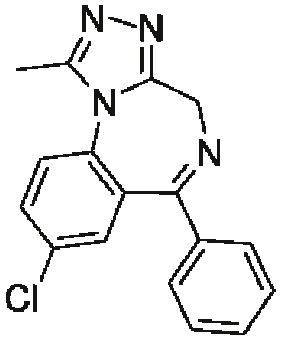
counterparts like Tricyclic antidepressants. He described the first group of patients treated by alprazolam as so impressed by its action. The company soon knew outright that the drug was going to be a hit. A few of those patients even pooled their money and purchased stock in Upjohn. Several months later in 1981, alprazolam was approved by the United States Food and Drug Administration and released. The company made a substantial profit.

Later in 1995, a Swedish Company, Pharmacia, acquired Upjohn. They continued the research on a longer acting Xanax, and developed the Xanax Extended Release (XANAX-XR) that comes in **0.5, 1, 2 or 3 mg**, with **just one dose per day**. Now, this product is made, marketed and sold by Pfizer Pharmaceuticals, which acquired Pharmacia and Upjohn in 2002.

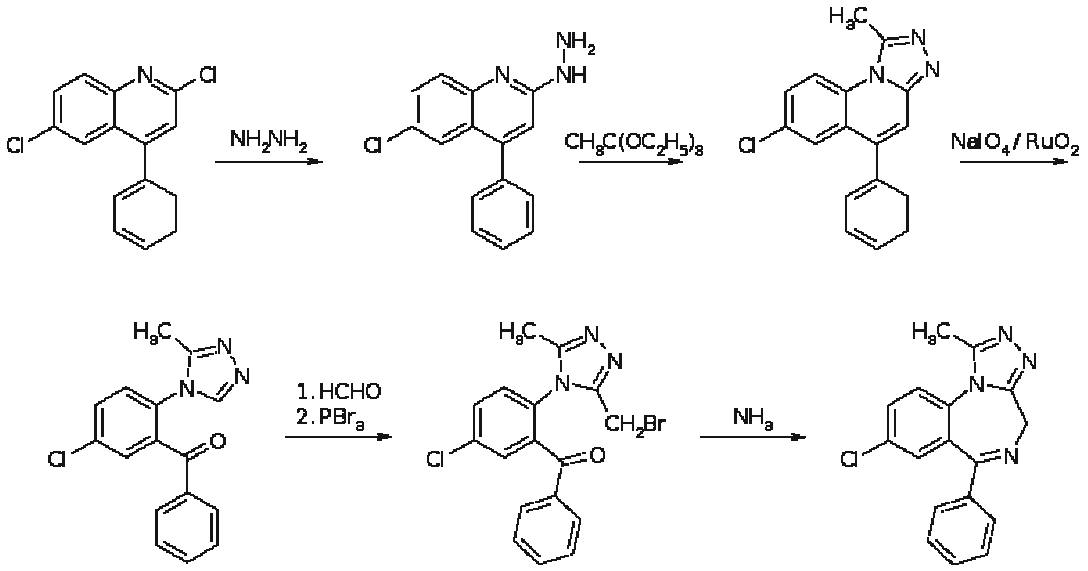
In fact, it is now one of the most prescribed psychotropic drugs and is **available under more than 40 brand names** on market nowadays. Mostly it is prescribed as "Xanax". However, in Latin-American Countries it is prescribed as "**Tafil**" or other brand names are used in other Countries.

II. Molecular modification

The IUPAC name of alprazolam is 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine, with molecular formula of alprazolam being $C_{17}H_{13}ClN_4$. Its molecular mass is 308.765. It exists in a white pill. It is **soluble in alcohol**, yet, it is **insoluble in water** and **does not readily cross the membranes**, thus, resulting in **reduced bioavailability**. The structural formula of alprazolam is as following:



Alprazolam is a chemical analog of triazolam. It differs by the absence of a chlorine atom in the *o*-position of the 6-phenyl ring. The synthesis of



alprazolam is similar to that of triazolam, with the exception that it begins with 2-amino-5-chlorobenzophenone. There still does not exist a standardized method to manufacture alprazolam. In common practice, 2,6-dichloro-4-phenylquinoline is used in the reaction with hydrazine to give 6-chloro-2-hydrazino-4-phynylquinoline. By boiling the product with triethyl orthoacetate in xylene, the heterocyclization is lead into a triazole derivative. Then, the product should undergo oxidative cleavage using sodium periodate and ruthenium dioxide in an acetone-water system so that 2-[4-(3′-methyl-1,2,4-triazolo)]-5-chlorobenzophenone is produced. Oxymethylation of the last using formaldehyde and subsequent substitution of the resulting hydroxyl group by phosphorus tribromide, thus, producing 2-[4-(3′-methyl-5′-bromomethyl-1,2,4-triazolo)]-5-chlorobenzophenone. Alprazolam is given in the substitution of the bromine atom with an amino group using ammonia and the spontaneous intramolecular heterocyclization.

III. Formulation Development

Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH. Each XANAX Tablet, for oral administration, contains 0.25, 0.5, 1 or 2 mg of alprazolam.

Active ingredients:	alprazolam
Inactive ingredients:	Cellulose Corn starch Docusate sodium Lactose Magnesium stearate Silicon dioxide Sodium benzoate

In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.

IV. Safety tests and human trials

Laboratory Tests

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice. Clinically, all benzodiazepines cause a **dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis**.

★ ***Gender***

Gender has **no effect** on the pharmacokinetics of alprazolam.

★ ***Cigarette Smoking***

Alprazolam concentrations may be **reduced by up to 50%** in smokers compared to non-smokers.

★ ***Pregnancy***

It should be considered that the child born of a mother who is receiving benzodiazepines may be **at some risk for withdrawal symptoms from the drug** during the postnatal period. Also, **neonatal flaccidity and respiratory problems** have been reported in children born of mothers who have been receiving benzodiazepines.

★ ***Nursing Mothers***

Benzodiazepines are known to be **excreted in human milk**. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their **infants to become**

lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use Xanax.

★ ***Pediatric Use***

Safety and effectiveness of Xanax in individuals **below 18 years of age have not been established.**

★ ***Geriatric Use***

The **elderly may be more sensitive** to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. **The smallest effective dose of Xanax should be used in the elderly** to preclude the development of ataxia and oversedation.

Human Trials

Although Xanax is a good invention to many patients suffering depression, there are still some side effects on their body. To minimize them, Xanax is refined.

Xanax was compared with Placebo in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. **Xanax was significantly better than placebo** at each of the evaluation periods of these **4-week studies** as judged by the following psychometric instruments: Physician's Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions and Self-Rating Symptom Scale.

The following are the results of the human trials. The table compares the percentage of the number of patients having the symptoms caused by taking Xanax, Placebo and the refined Xanax.

	Xanax	PLACEBO	Refined Xanax
Number of Patients % of Patients Reporting:	565	505	565
Central Nervous System			
Drowsiness	41.0	21.6	15.1
Light-headedness	20.8	19.3	1.2
Depression	13.9	18.1	2.4
Headache	12.9	19.6	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.9	18.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	/
Tiredness/Sleepiness	/	/	1.8

Gastrointestinal			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	2.4	/
Cardiovascular			
Tachycardia/Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	/
Sensory			
Blurred Vision	6.2	6.2	0.4
Musculoskeletal			
Rigidity	4.2	5.3	/
Tremor	4.0	8.8	0.4
Cutaneous			
Dermatitis/Allergy	3.8	3.1	0.6
Other			
Nasal Congestion	7.3	9.3	/
Weight Gain	2.7	2.7	/
Weight Loss	2.3	3.0	/

/ not reported

Given the above human trials, it is shown that Xanax caused fewer side effects than Placebo in most of the cases, while the refined Xanax caused even less effects. In conclusion, Xanax is a better drug than Placebo and the refined Xanax is better than Xanax.

V. Approval for marketing

Panic disorder was officially classified as a distinct psychiatric entity for the first time in 1980 by the American Psychological Association (APA)'s Diagnostic and Statistical Manual. Then, **in 1981**, the **U.S. Food and Drug Administration (FDA)** approved Xanax for the treatment of Panic Disorder.

Nowadays, Xanax is a famous medication indicated for panic disorder. There are many brands manufacturing it. For example, it is available under Alganax, Alzolam, Xanor, Xanax and so on.

Reference:

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