

**FLUNITRAZEPAM**



*"The Umbrellas", oil on canvas, 1883, Auguste Renoir, National Gallery, London.*

*Around 1703 the Swiss pigment and dye producer, Johan Jacob Diesbach, promised to prepare a batch of red cochineal dye for an important client. He was late in his commission, and so he was under considerable duress. He needed some potash to finish his product but all he had was some stock which he had marked out to be discarded as it had been contaminated with animal blood. Desperate to complete his task however, and having no other immediately available fresh potash, he simply shrugged his shoulders and went ahead and mixed in the contaminated potash. As blood was red, he thought, surely it would not too much influence the red cochineal in any case? He was wrong. To his utter amazement the resulting substance turned a most brilliant blue! Intrigued he experimented further, and found that the cochineal had been completely overwhelmed by a new pigment hitherto unknown. It appeared that the potash had reacted with the iron in the blood to produce, what would later be discovered, potassium ferrocyanide. The new pigment was cheap to produce, brilliant in its metallic luster, but most importantly of all it was much more light stable and so longer lasting than the traditional blue pigment, indigo. Prussian Blue became the first fully synthetic pigment developed in history.*

*Very quickly the new German Blue became de rigueur across Europe. Some of Europe's greatest Artists, including Jean Antoine Watteau began using it to produce stunning new works. The Venetian master Canaletto used it for his brilliant blue skies and waters in his Grand Canal pictures. So popular did German Blue become, it began to be used in fabrics. The Prussian Army no less, adopted it as the official colour for the uniforms of the infantry and artillery regiments, right up until the outbreak of World War I, when it was finally replaced by the familiar modern military khaki gray-green. So distinctive were the Prussian uniforms, the new German Blue became universally known as Prussian Blue. But it was in the visual Arts, that Prussian Blue most excelled. Brilliant new works whose blue pigments were far more light stable and so longer lasting than the older indigo pigment. It would truly come into its own during the great age of Impressionism in second half of the Nineteenth century.*

*If Watteau and Canaletto were the masters of Prussian Blue in the Eighteenth century, it would be August Renoir who would take blue to the next level in the Nineteenth, with ultramarine and another synthetic pigment, Cobalt Blue, developed in 1802. We see it over and over in his works, no more stunning example in his "Umbrellas" of 1883. This work was unusually complex in its evolution. X-ray studies of it have determined that it was essentially produced in two stages, the first around 1881 and second around 1883. X-ray images show the earlier version, and fashion historians are able to date these two periods astonishingly accurately on the style of dress of the milliner, the model of whom was the beautiful Suzanne Valadon, (herself a painter) who had begun posing for many of the Impressionists, Renoir in particular, at just 15 years of age.*

*Before the Impressionist age hardly any Artist had had the mind to see beauty in everyday scenes of nature. The Impressionists sought to capture the fleeting moments of nature, beautiful in its own right, devoid of any moral, religious or historical meaning. Edgar Degas and August Renoir, extended this sentiment to the city and as well as to its ordinary citizens. In the "Umbrellas" the life sized figures are caught in a sudden downpour of rain. In a flurry of activity a great bloom of blue umbrellas suddenly unfold. Renoir does capture the fleeting moment, the figures are not interacting with each other, rather each concentrates on protecting themselves from the rain. The "grisette" (working*

*class Parisian woman) glances at the young girl with a hoop, but makes no effort to protect her from the rain. The young girl herself ignores her playmate. The young gentleman to the left of the milliner who carries a bag of blue hats, seems about to gallantly offer her the protection of his umbrella, but she is quite oblivious to his attentions. However, despite the supposed chaos of the sudden downpour, Renoir connects us intimately with two of the figures. Disconnected to each other they may be, Renoir connects us intimately with two of them. The milliner looks back directly at the viewer a serene look in her eyes. The little girl with her hoop and iridescent blue hat looks almost mischievously back at the viewer as well. Renoir captures their serene personalities; a haunting calmness amidst the storm. Though Renoir was a committed Impressionist, he never completely abandoned more formal traditional forms.*

*The frantic pace of modern living frequently creates unexpected storms, indeed it seems at times that all of life is but a series of chaotic fleeting disconnected moments. Not much beauty in that anymore! The benzodiazepine agents were developed in an attempt to provide some calming temporary shelter amidst the storm of modern life. Like the Prussian Blue pigment, flunitrazepam, was developed for a longer lasting effect than its predecessors.*



## **FLUNITRAZEPAM**

### **Introduction**

**Flunitrazepam** (trade name in Australia “**Rohypnol**”, “**Hypnodorm**” among others) is a long acting benzodiazepine.

It is very commonly used as a nocturnal hypnotic.

As with all benzodiazepines this agent has potential for abuse and both psychological and physical dependence and do should be reserved for short term use only.

Flumazenil is the specific antidote to overdose of benzodiazepines.

**See also separate Documents on:**

- **Benzodiazepine overdose, (in Toxicology folder)**
- **Benzodiazepine withdrawal syndrome, (in Toxicology folder)**
- **Flumazenil, (in Drugs folder)**

### **History**

The first benzodiazepine chlordiazepoxide was discovered by Croatian-born Jewish American chemist **Leo Sternbach** in 1955.

The Swiss pharmaceutical company Hoffmann-La Roche introduced chlordiazepoxide to clinical practice as “Librium” in 1959.

Diazepam was the second benzodiazepine developed and was marketed as “Valium” in 1963. It was described as a “minor tranquilliser” (as an alternative to the barbiturates).

Flunitrazepam was developed at Roche as part of the benzodiazepine work led by **Leo Sternbach**. It was introduced into clinical practice in 1974.

By 1977 the benzodiazepines as a class were most the prescribed medications globally.

### **Chemistry**

**The Benzodiazepines** are a class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring.

### **Classification**

The benzodiazepines can be most usefully clinically classified according to their duration of action, as follows:



<b>Length of Action</b>	<b>Half-life</b>	<b>Drugs</b>
<b>Very short</b>	< 6 Hours	Midazolam, Triazolam.
<b>Short</b>	6-12 Hours	Temazepam, Oxazepam, Alprazolam.
<b>Medium</b>	12-24 Hours	Lorazepam, Bromazepam.
<b>Long</b>	> 24 Hours	Diazepam, Nitrazepam, Flunitrazepam, Clobazam, Clonazepam.

### Preparations

Flunitrazepam as:

Tablets:

- 1 mg.

### Mechanism of Action

The exact mechanism of action of the benzodiazepines is incompletely understood, but most current theories hold that they potentiate the action of the endogenous CNS inhibitory neurotransmitter gamma-aminobutyric acid (or **GABA**)

There are GABA-A and GABA-B receptors.

### Pharmacodynamics

As with most other benzodiazepine agents, principle effects include:

1. Anxiolysis
2. Sedation
3. Hypnotic
4. Skeletal muscle relaxant
5. Antiepileptic effects.

## 6. Anterograde amnesia

Flunitrazepam has marked sedative and hypnotic properties with a rapid onset of action.

### Pharmacokinetics

#### Absorption:

- Flunitrazepam is administered orally.  
It is almost completely absorbed.
- 10 - 15% is metabolized by a liver first-pass effect.

#### Distribution

- The distribution of flunitrazepam is rapid and extensive.
- About 80 % of absorbed flunitrazepam is bound to plasma proteins
- Flunitrazepam, like other benzodiazepines, is known to cross the placenta.
- Flunitrazepam is excreted into breast milk.

#### Metabolism and excretion:

- Flunitrazepam is extensively metabolized, and both the major metabolites, 7-amino-flunitrazepam and N-desmethyl- flunitrazepam, are pharmacologically active in humans but less so than the parent drug.

Both metabolites are eliminated as glucuronides, largely through the kidneys.

### Indications

Flunitrazepam is given for insomnia:

It should be reserved for short-term use only (e.g. 2 - 4 weeks); benzodiazepines should always be part of a broader treatment plan, not a first or sole treatment for insomnia.

### Contra-indications/precautions

For the benzodiazepines as a group, these include:

1. CNS depressant effects are synergistic with other CNS depressants including alcohol.
2. Chronic obstructive airways disease with incipient respiratory failure, particularly those who are CO<sub>2</sub> retainers.

3. Sleep apnea.
4. Contraindicated in myasthenia gravis.
5. Children and the elderly are more susceptible to the effects of benzodiazepines in general
6. Contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present. In mild-to-moderate impairment, use lower doses of a short-acting benzodiazepine to reduce risk of precipitating coma.
7. There is increased sensitivity to CNS effects in patients with severe renal impairment; use lower doses in severe impairment.
8. Known hypersensitivity to benzodiazepines or any of the components of the formulation
9. Caution must be exercised in prescribing any benzodiazepine to individuals known to be **addiction prone**.

### Pregnancy

Flunitrazepam is a category C drug with respect to pregnancy

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

There is very limited information available following the use of flunitrazepam during pregnancy.<sup>4</sup>

Flunitrazepam, like other benzodiazepines, is known to cross the placenta, and the limited studies to date do not suggest that there is increased risk of malformations in infants exposed to benzodiazepines in utero. Some case control studies have shown benzodiazepines exposure in early pregnancy may be associated with an increased risk of fetal cleft lip and cleft palate, while other studies have refuted these findings.

Maternal use of benzodiazepines may increase the risk of preterm birth and low birth weight. Infants may experience mild and transient neonatal withdrawal symptoms such as respiratory distress, restlessness, irritability and hypertonia. This 1 to 2 week period of self-limiting neonatal neuro-behavioural syndrome may present in the first 24 hours to several days after birth and may require supportive treatment.

Neonatal care providers should be informed about the maternal use of flunitrazepam as adverse effects or withdrawal signs may be present in newborns.

### Breast feeding

Compatible; caution with chronic use, monitor infant for drowsiness

Small amounts of flunitrazepam are excreted into breast milk, and chronic use may result in accumulation of the medicine in the breastfed infant.

Due to the long half-life of flunitrazepam, consider shorter acting benzodiazepines as an alternative during breastfeeding if possible.

In women who choose to breastfeed their healthy full-term infant while taking flunitrazepam, observe the breastfed infant for adverse effects such as drowsiness, poor feeding and sleeping pattern changes. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant. <sup>4</sup>

### Adverse Effects

General adverse effects of the benzodiazepines as a group include:

1. Excessive respiratory depression:
  - This is usually seen in association with other factors that impair respiratory drive, (e.g. COPD, other CNS depressants, sleep apnea)
2. Excessive somnolence/ CNS depression:
  - Usually in the setting of excessive dosing or when used in association with other CNS depressants.
3. Physical dependence:
  - A benzodiazepine withdrawal syndrome is possible.
  - Patients who have been on longer term therapy of benzodiazepines should not have these *abruptly* withdrawn.
4. Psychological dependence:
  - Paradoxical hyper-excitement reactions are rarely seen, (mainly children or elderly).
5. Tolerance:
  - Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, rarely occurs in patients receiving recommended doses under medical supervision.



- Tolerance may occur with longer term use, especially in those with drug seeking behaviour.
6. Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

### Dosing

Usual dosage is:

#### Adult:

- *Oral*, 0.5 - 2 mg at night.

#### Elderly:

- *Oral*, 0.5 - 1 mg at night.

### Reversal of effects:

Flumazenil is a specific benzodiazepine antagonist and will rapidly reverse the effects of benzodiazepines including depression of respiration and conscious state.



*Suzanne Valadon (1865-1938), c. 1883. Though a painter herself she also modelled for many of the Impressionists, including August Renoir, who depicted her as the milliner in his stunning “The Umbrellas” of 1881.*

### References

1. eTG - June 2017
2. Flunitrazepam in Australian Medicine's Handbook Website, Accessed July 2016.
3. Flunitrazepam in MIMs Website, 1 August 2007
4. RWH Pregnancy and Breastfeeding Guidelines, 3 March 2015.

Dr J. Hayes  
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