Swinol 1 mg Tablets

1. Name of the medicinal product

SWINOL

2. Qualitative and quantitative composition

Composition:
Each film-coated tablet contains:
Flunitrazepam……1 mg

3. Pharmaceutical form

Green oblong tablet embossed with breakscore above and Swinol® below Tablets

4. Clinical particulars

Flunitrazepam is a benzodiazepine used to manage anxiety disorders and insomnia.

4.1 Therapeutic indications

For short-term treatment of severe insomnias, that are not responsive to other hypnotics

4.2 Posology and method of administration

The recommended dosage for adult patients is 0.5-1 mg/day. In exceptional circumstances the dose may be increased to 2 mg. Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded. The product should be taken just before going to bed.

Duration of treatment:
Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to 2 weeks, with a maximum of 4 weeks including a tapering-off process.
In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without a re-evaluation of the patient's status. It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively
decreased. Moreover, it is important that the patient be made aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high .

Special dosage instructions:
Elderly:
The recommended dosage for elderly patients is 0.5 mg. In exceptional circumstances the dose may be increased to 1 mg.

Patients with hepatic impairment:
Patients with impaired liver function should receive a reduced dose.

Patients with chronic respiratory insufficiency:
A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression.

4.3 Contraindications

- myasthenia gravis
- use of this drug in patients with known hypersensitivity to flunitrazepam or to any of the components of the product
- hypersensitivity to benzodiazepines
- severe respiratory insufficiency
- sleep apnea syndrome
  children
- severe hepatic insufficiency

4.4 Special warnings and precautions for use

Benzodiazepines require special precaution if used in the elderly, during pregnancy, in children, in alcohol- or drug-dependent individuals, and in individuals with comorbid psychiatric disorders.

Impairment of driving skills with a resultant increased risk of road traffic accidents is probably the most important adverse effect. This side-effect is not unique to flunitrazepam but also occurs with other hypnotic drugs. Flunitrazepam seems to have a particularly high risk of road traffic accidents compared to other hypnotic drugs. Extreme caution should be exercised by drivers after taking flunitrazepam

4.5 Interaction with other medicinal products and other forms of interaction

Benzodiazepine
The risk or severity of CNS depression can be increased when Flunitrazepam is combined with 1,2-Benzodiazepine.

Abacavir
The metabolism of Abacavir can be decreased when combined with Flunitrazepam

Abametapir
The serum concentration of Flunitrazepam can be increased when it is combined with Abametapir.

Abatacept
The metabolism of Flunitrazepam can be increased when combined with Abatacept

Abrocitinib
The metabolism of Abrocitinib can be decreased when combined with Flunitrazepam

Acemetacin
The metabolism of Acemetacin can be decreased when combined with Flunitrazepam

Acenocoumarol
The metabolism of Flunitrazepam can be decreased when combined with Acenocoumarol

Acetaminophen
Flunitrazepam may increase the hepatotoxic activities of Acetaminophen.

Acetazolamide
The risk or severity of CNS depression can be increased when Acetazolamide is combined with Flunitrazepam.

Acetohexamide
The metabolism of Flunitrazepam can be decreased when combined with Acetohexamide

Acetylsalicylic acid.
The metabolism of Flunitrazepam can be decreased when combined with Acetylsalicylic acid.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There is no evidence as to drug safety in human pregnancy, nor is there evidence from animal work that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

Administration of benzodiazepines in the last trimester of pregnancy or during labour has been reported to produce irregularities in the foetal heart rate, and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate.

Infants born to mothers who took benzodiazepines chronically in the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Breast-feeding:

Since benzodiazepines are found in the breast milk, the use of Swinol in mothers who are breast-feeding should be avoided.

4.7 Effects on ability to drive and use machines

Patients should be advised that, like all medicaments of this type, Swinol may modify patients' performance at skilled tasks. Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or use machinery. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients should further be advised that alcohol may intensify any impairment, and should therefore be avoided during treatment.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and

- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

- It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse effects of flunitrazepam include dependency, both physical and psychological; reduced sleep quality resulting in somnolence; and overdose, resulting in excessive

sedation, impairment of balance and speech, respiratory depression or coma, and possibly death. Because of the latter, flunitrazepam is commonly used in suicide. When used in late pregnancy, it might cause hypotonia of the fetus.

Dependence

Flunitrazepam, as with other benzodiazepines, can lead to drug dependence. Discontinuation may result in benzodiazepine withdrawal syndrome, characterised by seizures, psychosis, insomnia, and anxiety. Rebound insomnia, worse than baseline insomnia, typically occurs after discontinuation of flunitrazepam even from short-term single nightly dose therapy.

Paradoxical Effect

Flunitrazepam may cause a paradoxical reaction in some individuals, including anxiety, aggressiveness, agitation, confusion, disinhibition, loss of impulse control, talkativeness, violent behavior, and even convulsions. Paradoxical adverse effects may even lead to criminal behaviour.

Hypotonia

Benzodiazepines such as flunitrazepam are lipophilic and rapidly penetrate membranes and, therefore, rapidly cross over into the placenta with significant uptake of the drug. Use of benzodiazepines including flunitrazepam in late pregnancy, especially high doses, may result in hypotonia, also known as floppy baby syndrome.

Flunitrazepam impairs cognitive functions. This may appear as lack of concentration, confusion and anterograde amnesia—the inability to create memories while under the influence. It can be described as a hangover-like effect which can persist to the next day. It also impairs psychomotor functions similar to other benzodiazepines and nonbenzodiazepine hypnotic drugs; falls and hip fractures were frequently reported. The combination with alcohol increases these impairments. Partial, but incomplete tolerance develops to these impairments.

Other adverse effects include:

- Slurred speech
- Gastrointestinal disturbances, lasting 12 or more hours
- Vomiting
- Respiratory depression in higher doses

4.9 Overdose

Flunitrazepam has a long half-life of 18 - 26 hours and an active metabolite which has a half life of 36-200 hours, which means flunitrazepam effects after nighttime administration persist throughout the next day. Residual 'hangover' effects after nighttime administration of flunitrazepam such as sleepiness, impaired psychomotor and cognitive may persist into the next day which may impair the ability of users to drive safely and increase risks of falls and hip fractures.

Flunitrazepam is lipophilic and is metabolised hepatically via oxidative pathways. The enzyme CYP3A4 is the main enzyme in its phase 1 metabolism.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Flunitrazepam is a powerful hypnotic drug that is a benzodiazepine derivative. It has

powerful hypnotic, sedative, anxiolytic, and skeletal muscle relaxant properties. The drug is sometimes used as a date rape drug. In the United States, the drug has not been approved by the Food and Drug Administration for medical use, and is considered to be an illegal drug. It has however been approved in the United Kingdom and other countries.
Benzodiazepines bind nonspecifically to benzodiazepine receptors BNZ1, which mediates sleep, and BNZ2, which affects muscle relaxation, anticonvulsant activity, motor coordination, and memory. As benzodiazepine receptors are thought to be coupled to gamma-aminobutyric acid-A (GABAA) receptors, this enhances the effects of GABA by increasing GABA affinity for the GABA receptor. Binding of the inhibitory neurotransmitter GABA to the site opens the chloride channel, resulting in a hyperpolarized cell membrane that prevents further excitation of the cell.

5.2 Pharmacokinetic properties

While 80% of flunitrazepam that is taken orally is absorbed, bioavailability in suppository form is closer to 50%. Benzodiazepines such as flunitrazepam are lipophilic and rapidly penetrate membranes.

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Absorption
Following oral administration, flunitrazepam is almost entirely absorbed. 10-15% undergoes first-pass metabolism in the liver resulting in an absolute (vs. intravenous solution) bioavailability of 70-90%. The maximum plasma concentrations of flunitrazepam are 6-11 ng/ml and occur 0.75 -2 hours after administration of a single oral dose of 1 mg on an empty stomach. Food reduces the rate and extent of flunitrazepam absorption. The pharmacokinetics of flunitrazepam are linear in the 0.5-4 mg dose range. Repetitive daily oral administrations lead to a moderate accumulation of flunitrazepam in plasma (accumulation ratio 1.6-1.7).The steady state plasma concentration of flunitrazepam is reached after 5 days. The minimum plasma concentration of flunitrazepam at steady state is 3-4 ng/ml following multiple oral doses
of 2 mg. The steady state plasma concentration of the pharmacologically active N-desmethyl metabolite is almost identical to that of the parent compound.

Distribution:
The distribution of flunitrazepam is rapid and extensive. The volume of distribution at steady state is 3-5 liters/kg. Flunitrazepam is 78% bound to plasma proteins. There is a rapid uptake of flunitrazepam into human cerebrospinal fluid. Flunitrazepam crosses the human placenta and blood-milk barrier slowly and to a minor extent after a single dose.

Metabolism and Elimination:

Flunitrazepam is almost completely metabolized. About 80% and 10% of the radiolabelare found in urine and faeces, respectively. The principal plasma metabolites are 7-amino-flunitrazepam and N-desmethyl-flunitrazepam. The major urinary metabolite is 7-amino-flunitrazepam. Less than 2% of a dose is excreted renally as unchanged drug and as N-desmethyl-flunitrazepam.
pharmacologically active in man, though less than flunitrazepam, and plasma levels at steady state resulting from daily doses of 2 mg flunitrazepam are below the minimum effective concentration of the metabolite.
The elimination half-life of flunitrazepam is between 16 and 35 hours. The half-life of the active N-desmethyl-flunitrazepam is 28 hours. The total plasma clearance is 120-140 ml/min

5.3 Preclinical safety data

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

Avicel Ph 101, Lactose powder, Kollidon 90F, FD&C blue, hydroxypropyl methyl Cellulose, Croscarmellose sodium, Magnesium stearate and Green coating material.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

The recommended maximum storage temperature for Swinol tablets is 30°C.

All packs should be protected from light and the blister packs should be protected from moisture i.e., stored in a dry place.

6.5 Nature and contents of container

SWINOL Tablets are packed in a strip foil of 3 x 10 tablets.

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6.6 Special precautions for disposal and other handling

Any unused product should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

SWISS PHARMA NIGERIA LTD

5 Dopemu Road, Agege,

Lagos,

Nigeria.

8. Marketing authorisation number(s)

Company Contact Details

SWISS PHARMA NIGERIA LTD

5 Dopemu Road, Agege,

Lagos,

Nigeria

Phone: +2348116691559

Email: swipha@swiphanigeria.com

Website: www.swiphanigeria.com