1. NAME OF THE MEDICINAL PRODUCT

Antezin Elixir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains Piperazine Hydrate 750mg.
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Antezin Elixir is presented as clear, orange coloured syrup for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The product is indicated in the treatment for ascariasis caused by *Ascaris lumbricoides* (roundworm) and enterobiasis (oxyuriasis) caused by *Enterobius vermicularis* (pinworm, threadworm). Piperazine is especially useful in the treatment of partial intestinal obstruction caused by *Ascaris* worms, which is a condition primarily seen in children

4.2 Posology and method of administration

Posology
Doses are expressed in terms piperazine hydrate.

For the treatment of ascariasis, a single dose repeated once after 14 days, has been used. In adults and children over 12 years of age, a dose equivalent to 4.5g of piperazine hydrate is given orally.
For enterobiasis, piperazine has been given for 7 days. A second course after a 7-day interval may be required.
Adults and children over 12 years of age are given the equivalent of 2.25g of the hydrate once daily.

Administration in children:
Piperazine may be given orally to children for the treatment of intestinal nematode infections such as ascariasis (roundworm) and enterobiasis (pinworm and threadworm)

Treatment of ascariasis
A single dose equivalent to the following amount of piperazine hydrate is given, repeated once after 14 days
9 to 12 years of age: 3.75g
6 to 8 years of age: 3g
4 to 5 years of age: 2.25g
1 to 3 years of age: 1.5g
Under 1 year of age (on medical advice only)**:** 120mg/kg has been suggested.
Treatment of enterobiasis
Piperazine has been given for 7 days in doses equivalent to the following amount of piperazine hydrate.

7 to 12 years of age: 1.5g daily
4 to 6 years of age: 1.125g daily
1 to 3 years of age: 750mg daily
Under 1 year of age (on medical advice only)**:** 45 to 75mg/kg daily has been suggested.

A second course of treatment after a 7-day interval may be required.

Renal Impairment
Piperazine should be given with care to patients with mild to moderate renal impairmrnt and contra-indicated in patients with severe renal impairment.
Hepatic Impairment
Piperazine should be avoided or given with extreme caution in patients with hepatic impairment.

Method of administration
Antezin Elixir is for Oral administration.
Piperazine may be taken with or without food or on a full or empty stomach. However, the drug should be taken only as directed by the physician. Duration of therapy should be appropriate to the indication and should not exceed the prescribed dose by the physician.

4.3 Contraindications

- Antezin is contraindicated in patients with a known history of piperazine hypersensitivity or to any of the excipients.
- Patients with history of epilepsy
- Patients with severe renal impairment
- Patients with hepatic impairment
- Contraindicated in pregnancy especially during the first trimester

4.4 Special warnings and precautions for use

- Piperazine should be given with care to patients with chronic disorders of the central nervous system such as neurological disturbances.
- Use with caution in patients with severe malnutrition and anaemia. In ascariasis, if the patient has normal bowel movements, a purgative is not necessary but if patient is constipated, it is necessary to purge the patient about 12 hours after treatment so that the worms are expelled before the effects of the drug wears off.

4.5 Interaction with other medicinal products and other forms of interaction

Pyranthel - The anthelminthic effects of piperazine and pyrantel may be antagonised when the two compounds are used together and therefore should not be co-administered.
Phenothiazines - Taking piperazine may potentiate the extrapyramidal effects in patients receiving phenothiazines and may increase the risk of convulsions (seizures), concurrent use is not recommended.

4.6 Pregnancy and lactation

Pregnancy
Adequate and well-controlled studies in humans have not been done. Piperazine has been used without apparent adverse effects during pregnancy. In three cases of first-trimester exposures to piperazine by pregnant women, no malformations were seen in the fetuses. However, because a study showed that orally administered piperazine undergoes partial conversion to a potentially carcinogenic nitrosamine derivative, it is recommended that piperazine be given to pregnant women only if clearly indicated and then only if alternative medications are not available. Piperazine should not be given at any time during pregnancy except on medical advice.
It has been reported that piperazine is teratogenic in rabbits and that there have been isolated reports of foetal malformations after clinical use, though causal relationship has been established. Two infants with malformations have been described briefly. Both mothers had taken a preparation containing piperazine and senna.
Lactation
Piperazine is thought to be distributed into breast milk but no definitive information is available. However, problems in humans have not been documented. Mothers are advised to take a dose after breastfeeding then not to breast feed for 8 hours during which period milk should be expressed and discarded at the regular feeding times.

Paediatrics

Appropriate studies on the relationship of age to the effects of piperazine have not been performed in the pediatric population. No pediatrics-specific problems have been documented to date. However, because of piperazine's potential neurotoxicity, it should be used with caution in children. Prolonged or repeated treatment with piperazine in children should be avoided.

Geriatrics

No information is available on the relationship of age to the effects of piperazine in geriatric patients.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Serious adverse effects are rare with piperazine and generally indicate overdosage or impaired excretion. In the recommended dosage side-effects are not common but the following have been reported: Gastro-intestinal disturbance Drowsiness, confusion, ataxia, reduced muscle tension Clonic contractions have occurred but are only likely if neurological abnormalities or renal disease exist. Abdominal cramps, headaches, dizziness, tremors, choreirform movements, hyporeflexia, nystagmus, seizures, blurred vision, paralytic strabismus and rarely, cataracts. Allergic reactions occasionally encountered include: Skin reactions, arthralgia, fever, oedema and tachycardia. Urticaria, photodermatitis, erythema multiforme, purpura, eczematous skin reactions, lacrimation, rhinorrhoea and rarely, broncospasm.
The following convention has been used for the classification of frequency:

very common >1/10
common >1/100 and <1/10
uncommon >1/1000 and <1/100
rare >1/10,000 and <1/1000
very rare <1/10,000. 7

Gastrointestinal disorders
Uncommon: Nausea, vomiting, diarhoea, abdominal pain

Nervous system disorders
Uncommon: Headache
Rare: Neurotoxicity and EEG abnormalities, somnolence, dizziness, nystagmus, muscular incoordination and weakness, ataxia, paraesthesia, myoclonic contractions, choreiform movements, tremor, convulsions and loss of reflexes.

Skin and subcutaneous tissue disorders
Uncommon: Skin rash, urticaria

Visual disorders
Very rare (unsubstantiated reports): Transient visual disturbances such as blurred vision, cataract formation

Immune system disorders
Very rare: Bronchospasm, Stevens-Johnson syndrome and angioedema.

4.9 Overdose

Symptoms and signs of overdose:
Within the specific dosage regimen piperazine is safe with little or no toxic effect but in overdosage toxicity has been determined such as nausea, vomiting abdominal pain, diarrhoea, impaired consciousness, muscle hypotonia, clonic contractions, ataxia, precipitation of grand mal epilepsy, diplopia and myoclonus and difficulty in breathing.

Toxicity
LD_{50} = 5 g/kg (Human, oral).

Treatment of Overdosage:
In view of the rapid absorption of piperazine, gastric lavage should only be considered within the first two (2) hours of ingestion. Adequate fluids should be given to ensure optimal diuresis. Routine supportive measures, including the administration of anti-convulsants should be given when necessary. In patients with renal insufficiency, haemodialysis is more effective than peritoneal dialysis in the treatment of piperazine toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Piperazine is an anthelminthic effective against the intestinal nematodes Ascaris lumbricoides (roundworm) and Enterobius vermicularis (pinworm, threadworm)

Mechanism of Action
In roundworms piperazine produces muscle paralysis and the worms are then expelled with the faeces. Piperzine affects all stages of roundworm in the gut.
Piperazine is a GABA receptor agonist. Piperzine binds directly and selectively to muscle membrane GABA receptors thereby blocking response of the worm muscle to acetylcholine, presumably causing hyperpolarization of nerve endings, resulting in flaccid paralysis of the worm. While the worm is paralyzed, it is dislodged from the intestinal lumen and expelled live from the body by normal intestinal peristalsis. The neuromuscular effects are thought to be caused by blocking acetylcholine at the myoneural junction apparently by altering the permeability of the cell membrane to ions that are responsible for the maintenance of the resting potential. The drug causes hyperpolarization and suppression of spontaneous spike potentials with accompanying paralysis.
This action is mediated by its agonist effects upon the inhibitory GABA (γ-aminobutyric acid) receptor. Its selectivity for helminths is because vertebrates only use GABA in the CNS and the helminths GABA receptor is a different isoform to the vertebrates' one.
The mode of action of piperazine on threadworm is not fully understood.

Spectrum
Piperazine is active against susceptible intestinal nematodes Ascaris lumbricoides (roundworm) and Enterobius vermicularis (pinworm, threadworm).

5.2 Pharmacokinetic properties
Piperazine is readily absorbed from the gastro intestinal tract. A portion of the absorbed drug is degraded and the remainder is excreted in the urine within 24 hours, partly as metabolites. About 25% is metabolized in the liver. Piperazine is nitrosated to form N -mononitrosopiperazine (MNPz) in gastric juice, which is then metabolized to N-nitroso-3-hydroxypyrrolidine (NHPYR). After a single oral dose of Piperazine, urinary excretion of piperazine begins during the first hour, reaches a maximum between the second and sixth hour and is nearly complete by the 24th hour. Piperazine has pKa of 5.6 and 9.8 at 25^0C. The rate at which different individuals excrete piperazine has been reported to vary widely. It is distributed into breast milk.
No significant difference between the rates of urinary excretion of the citrate, phosphate and adipate.

5.3 Preclinical safety data

No further information of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Methyl Hydroxybenzoate, Sodium Benzoate, sucrose, citric acid anhydrous, FD & C Yellow No. 6 (Soluble Usacert), Pineapple flavour, Purified Water.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Product should be stored in a cool, dry place under 30^oC and protected from light.

6.5 Nature and contents of container

30ml Amber coloured PET bottles with aluminium screw caps supplied with a measuring cup dosing device.

6.6 Special precautions for disposal and other handling

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

7 APPLICANT/MANUFACTURER

SKG-Pharma Limited
7/9 Sapara Street,
Ikeja, Lagos State, Nigeria.
Tel: +234(1)44544640
Email: skgpharma@yahoo.com