SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ZIZ Extra Strength

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of the active substance Promethazine hydrochloride.

Excipient (s) with known effects
Also contains 35.44 mg of lactose and 51.50mg of sucrose.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sugar-coated tablet

Blue sugar-coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As symptomatic treatment of allergic conditions of the upper respiratory tract and skin: including allergic rhinitis, urticaria and anaphylactic reactions to drugs or foreign proteins
As an antiemetic.
For short term use:
- Treatment of insomnia in adults.
- As a paediatric sedative.

4.2 Posology and method of administration

Route of administration: Oral

Paediatric population:
Not for use in children under the age of 6 years because the safety of such use has not been established.

As an antihistamine in allergy:

Children 6-10 years	25 mg as a single dose*.

	Maximum daily dose 25 mg.
Children over 10 years and adults (including elderly)	25 mg as a single dose*. Increasing to a maximum of 25 mg twice a day as required.

*Single doses are best taken at night.

As an antiemetic:

Children 6-10 years	The use of Promethazine liquid or Promethazine 10mg tablet indicated as an antiemetic is suitable.
Children over 10 years and adults (including elderly)	25 mg to be taken the night before the journey To be repeated after 6-8 hours as required.

As a paediatric sedative for short-term use and for short term treatment of insomnia in adults:

Children 6-10 years	25 mg given as a single night-time dose.
Children over 10 years and adults (including elderly)	One 25 mg tablet at night may be increased to two 25 mg tablets at night if necessary.

4.3 Contraindications

Ziz Extra strength should not be given to patient with a known hypersensitivity to the active substance, other promethazine or to any of the excipients listed in section 6.1.

Ziz Extra Strength should not be used in patients:

- in coma or
- suffering from CNS depression of any cause or,

Ziz Extra Strength is contraindicated for use in children less than 6 years (see Section 4.4).

Ziz Extra Strength should be avoided in patients taking monoamine oxidase inhibitors up to 14 days previously.

4.4 Special warnings and precautions for use

Hypersensitivity reactions including anaphylaxis, urticaria and angioedema have been reported with Promethazine use. In case of allergic reaction, treatment with Promethazine must be discontinued and appropriate symptomatic treatment initiated (see Section 4.8).

Promethazine should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, pheochromocytoma,

myasthenia gravis, or prostate hypertrophy, or in patients with a history of narrow angle glaucoma or agranulocytosis.

Caution must be exercised when using H1-antihistamines such as Promethazine due to the risk of sedation. Combined use with other sedative medicinal products is not recommended (see section 4.5).

Promethazine should not be used for more than 7 days without seeking medical advice.

Caution should be used in patients with:
• asthma, bronchitis or bronchiectasis. Promethazine may thicken or dry lung secretions and impair expectoration.
• Severe coronary artery disease
• Epilepsy
• Bladder neck or pyloro-duodenal obstruction

Therefore caution should be exercised in patients who might be at risk from the anti-cholinergic actions of the drug, including those with asthma, bronchitis or bronchiectasis.
Use with caution in patients with severe coronary disease, narrow angle glaucoma, epilepsy, urinary retention or hepatic and renal insufficiency.

Caution should be exercised in patients with prostatic hypertrophy and bladder neck or pyloro-duodenal obstruction.

There have been case reports of drug abuse with promethazine. The risk of abuse is greater in patients with a history of drug abuse.

As with neuroleptics, Neuroleptic Malignant Syndrome (NMS) characterized by hyperthermia, extrapyramidal disorders, muscle rigidity, altered mental status, autonomic nervous instability and elevated CPK, may occur. As this syndrome is potentially fatal, promethazine must be discontinued immediately and intensive clinical monitoring and symptomatic treatment should be initiated.

Ototoxicity

Promethazine may mask the warning signs of ototoxicity caused by ototoxic drugs e.g. salicylates. It may also delay the early diagnosis of intestinal obstruction or raised intracranial pressure through the suppression of vomiting.

QT interval

As phenothiazines can prolong the QT interval, caution is advised in treated patients with pronounced bradycardia, cardiovascular disease, with a hereditary form of prolongation of the QT interval and concomitant use with other products leading to QT prolongation.

QT prolongation

Phenothiazine derivatives may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalaemia, and acquired (i.e. drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a phenothiazine derivative and as deemed necessary during treatment (see section 4.8).

Photosensitivity reactions

Due to the risk of photosensitivity, exposure to strong sunlight or ultraviolet light should be avoided during or shortly after treatment (see section 4.8).

Paediatric population

ZIZ Extra Strength must not be used in children less than six years of age due to the potential for fatal respiratory depression, psychiatric and CNS events (see Section 4.3 and Section 4.8)

The use of ZIZ Extra Strength should be avoided in children and adolescents with signs and symptoms suggestive of Reye's Syndrome.

Excipient(s) with known effect

This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Alcohol and alcohol-containing medicines should be avoided while on this medicine (see section 4.5).

ZIZ Extra Strength may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, general anesthetics, or alcohol.

The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see section 4.8) and requires immediate hematological investigation.

All patients should be advised that, if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.

4.5 Interaction with other medicinal products and other forms of interaction

ZIZ Extra Strength will enhance the action of any anti-cholinergic agent, tricyclic anti-depressant, sedative, hypnotic.

Alcohol should be avoided during treatment. Combination with alcohol enhances the sedative effects of H1 antihistamines.

ZIZ Extra Strength may interfere with immunological urine pregnancy tests and cause false- positive or false-negative results.

ZIZ Extra Strength should be discontinued at least 72 hours before the start of skin tests as it may inhibit the cutaneous histamine response and thus producing false-negative results.

Special caution is required when promethazine is used concurrently with other products leading to QT prolongation, including medicinal products such as antipsychotics, i.e., some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, amisulpride, tiapride), pimozide, haloperidol, droperidol, citalopram, halofantrin, methadone, pentamidine, and moxifloxacine.

Special caution is required when promethazine is used concurrently with drugs known to cause QT prolongation (such as antiarrhythmics, antimicrobials, antidepressants, to avoid exacerbation of risk of QT prolongation.

Cytochrome P450 2D6 Metabolism: Some phenothiazines are moderate inhibitors of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co administration of ZIZ Extra Strength with amitriptyline/amitriptylinoxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline/amitriptylinoxide. Monitor patients for dose-dependent adverse reactions associated with amitriptyline/amitriptylinoxide.
ZIZ Extra Strength should be avoided in patients taking monamine oxidase inhibitors within the previous 14 days, and monamine oxidase inhibitors should be avoided while using ZIZ Extra Strength.

Seizure threshold-lowering drugs: Concomitant use of seizure-inducing drugs or seizure threshold-lowering drugs should be carefully considered due to the severity of the risk for the patient (see section 4.4).

Gastro-intestinal agents that are not absorbed (magnesium, aluminium and calcium salts, oxides and hydroxides): Reduced gastro-intestinal absorption of phenothiazines may occur. Such gastro-intestinal agents should not be taken at the same time as phenothiazines (at least 2 hours apart, if possible).

Drugs with anticholinergic properties: Concomitant use of ZIZ Extra Strength with drugs with anticholinergic properties enhances the anticholinergic effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ZIZ Extra Strength is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the potential benefits outweigh the potential risks. When ZIZ Extra Strength has been given in high doses during late pregnancy, ZIZ Extra Strength has caused prolonged neurological disturbances in the infant.

ZIZ Extra Strength should not be used in pregnancy unless the physician considers it essential. The use of ZIZ Extra Strength is not recommended in the 2 weeks prior to delivery in view of the risk of irritability and excitement in the neonate.

Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise patients to avoid becoming pregnant while receiving this medicine. Advise female patients of reproductive potential to use effective contraception.

There are no available animal studies regarding reproductive toxicity.

Breast feeding

Available evidence suggests that the amount of ZIZ Extra Strength excreted in breast milk is insignificant. However, there are risks of neonate irritability and excitement. ZIZ Extra Strength is not recommended for use in breast-feeding.

Fertility

There are no relevant fertility data in animals.

4.7 Effects on ability to drive and use machines

Because the duration of action may be up to 12 hours, patients should be advised that if they feel drowsy, dizzy and have blurred vision, they should not drive or operate heavy machinery.

4.8 Undesirable effects

The following CIOMS frequency rating is used: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 00 to <1/1000); very rare (<1/10 000), not known (cannot be estimated from the available data).

Immune system disorders
Not known: Allergic reactions, including urticaria, angioedema, rashes, pruritus, and anaphylactic reactions have been reported.

Skin and subcutaneous tissue disorders
Not known: Rash and photosensitivity reactions have been reported; strong sunlight should be avoided during treatment.

Nervous system disorders
Very common: Sedation or somnolence
Not known: Dizziness, headaches, extrapyramidal effects including restless legs syndrome, muscle spasms and tic-like movements of the head and face, neuroleptic

Malignant Syndrome, psychomotor hyperactivity.

Not known: Dystonia, including oculogyric crisis, usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.

Not known: Anticholinergic effects such as ileus paralytic, accommodation disorder.
The elderly are more prone to the anti-cholinergic effects and confusion due to promethazine.

Not known: children less than 6 years of age also experienced psychomotor hyperactivity.

Psychiatric disorders

Not known: Agitation, confusional state, anxiety, hallucinations, aggression.
Not known: Infants, newborns and premature are susceptible to the anticholinergic effects of promethazine, while other children may display paradoxical hyperexcitability, restlessness, nightmares, disorientation

Not known: children less than 6 years of age also experienced aggression and hallucination.

Eye disorders
Not known: blurred vision.

Gastrointestinal disorders
Not known: Epigastric irritation/ discomfort, dry mouth

Renal and urinary disorders
Not known: urinary retention

Metabolism and nutrition disorders
Not known: Decreased appetite, anorexia

Cardiac disorders
Not known: palpitations, arrhythmias, QT prolongation, torsade de pointes

Vascular disorders
Not known: hypotension

Respiratory, thoracic and mediastinal disorders
Not known: Respiratory depression (see Section 4.4), nasal congestion

Hepatobiliary disorders
Not known: Jaundice cholestatic

Blood and lymphatic system disorders
Not known: Blood dyscrasias including haemolytic anaemia, agranulocytosis, leukopenia, eosinophilia, thrombocytopenia (including thrombocytopenic purpura).

General disorders and administration site conditions
Not known: Tiredness
Anaphylaxis, liver dysfunction rarely occur.
Hypersensitivity reactions include liver dysfunction ,

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
The symptoms of severe overdose are variable. They are characterised in children by various combinations of excitation, ataxia, incoordination, athetosis and hallucinations, intellectual disability and cognition deficit in children less than 6 years of age while adults may become drowsy and lapse into coma. Convulsions may occur in both adults and children; coma or excitement may precede their occurrence. Tachycardia may develop. Cardio-respiratory depression is uncommon.

High doses (supratherapeutic doses) can cause ventricular arrhythmias including QT prolongation and torsade de pointes (see section 4.8).

Prolonged QT interval and cases of severe arrhythmias with fatal outcome have been described in overdose of phenothiazines.

Management
If the patient is seen soon enough after ingestion, it should be possible to induce vomiting with ipecacuanha despite the anti-emetic effect of Promethazine; alternatively, gastric lavage may be used.

Treatment is otherwise supportive with attention to maintenance of adequate respiratory and circulatory status. Convulsions should be treated with Diazepam or other suitable anticonvulsant.

In the event of overdose of ZIZ Extra Strength, take all appropriate measures immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use; Phenothiazine derivatives, ATC code: R06AD02

Potent, long acting, antihistamine with additional anti-emetic central sedative and anti-cholinergic properties.

5.2 Pharmacokinetic properties

ZIZ extra Strength is distributed widely in the body. It enters the brain and crossed the placenta. ZIZ is slowly excreted via urine and bile.Phenothiazines pass into the milk at low concentrations.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:	Lactose Maize Starch Pregelatinised Maize Starch Magnesium Stearate
Coating:	Bleached Shellac Talc, purified Povidone Opalux Blue AS-F-4312G (contains Indigo Carmine E132, Patent Blue E131, Titanium Dioxide (E171) Sodium Benzoate (E211) Sucrose Beeswax Carnauba Wax

6.2 Incompatibilities

Promethazine Hydrochloride is incompatible with alkaline substances, which precipitate Promethazine Base.

6.3 Shelf life

Polystyrene/polypropylene containers - 36 months

PVC/Aluminium strips - 24 months

6.4 Special precautions for storage

Containers:	Do not store above 25°C. Keep the container tightly closed. Store in the original container.
Strips:	Do not store above 25°C. Store in the original package. Keep the blister in the outer carton.

6.5 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane/polythene inserts.

Packs of 100, 500 and 1000 tablets.

PVC/Aluminium foil strips.

Packs of 10, 30 and 56 tablets.

6.6 Special precautions for disposal

No special precautions.

7 MARKETING AUTHORISATION HOLDER

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PL 33414/0147

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