Xyquil® XR Forte

(Doxylamine Succinate + Pyridoxine HCl)

1. NAME OF THE PRODUCT

Xyquil® XR Forte (Doxylamine Succinate + Pyridoxine HCl) 20mg/20mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Xyquil® XR Forte 20mg/20mg Tablet

Each film coated extended release tablet contains:
Doxylamine Succinate.....10mg
Pyridoxine Hydrochloride.....10mg
(as Enteric Coated Core)
Doxylamine Succinate.....10mg
Pyridoxine Hydrochloride.....10mg
(as Immediate Release Core)

3. PHARMACEUTICAL FORM

Modified-release tablet

Appearance: Pink colored, round shaped film coated tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Xyquil® XR Forte is indicated for the symptomatic treatment of nausea and vomiting of pregnancy (NVP) in pregnant women ≥18 years who do not respond to conservative management (i.e., lifestyle and diet change).

Limitations of use: The combination doxylamine/pyridoxine has not been studied in case of hyperemesis gravidarum.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology:

The recommended starting dose of **Xyquil® XR Forte** is one tablet (20mg/20mg) at bedtime on Day 1 and on Day 2. If symptoms are not adequately controlled on Day 2, the dose can be increased on Day 3 to one additional tablet (20mg/20mg) in the morning and one tablet (20mg/20mg) at bedtime (for a total of two tablets per day). The maximum recommended dose is two tablets daily, one in the morning and one at bedtime (for a maximum daily dose of 40mg/40mg). **Xyquil® XR Forte** be taken as a daily prescription and not on an

as needed basis. Continued need for **Xyquil®XR Forte** should be reassessed as the pregnancy progresses.
Some women may achieve symptom control at intermediatory doses of 30mg/30mg. This dose is not achievable with **Xyquil®XR Forte** 20mg/20mg. Other formulations of doxylamine succinate/pyridoxine hydrochloride are available which provide for greater flexibility to dose adjust according to severity of symptoms. With **Xyquil®XR Forte** modified-release tablet formulation, the maximum daily recommended dosing of 40mg/40mg consists of only two tablets daily.
To prevent a sudden return of nausea and vomiting of pregnancy symptoms, a gradual tapering dose of **Xyquil®XR Forte** is recommended at the time of discontinuation.
Hepatic impairment: No pharmacokinetic studies have been conducted in hepatic impaired patients. Caution is however recommended due to potential for reduced metabolism; there is a possibility of dosage adjustment.
Renal impairment: No pharmacokinetic studies have been conducted in renal impaired patients. Caution is however recommended due to potential for metabolite accumulation; there is a possibility of dosage adjustment.
Paediatric population: Xyquil®XR Forte is not recommended for use in children under 18 years of age, due to lack of clinical data.

Method of administration:
For oral use.
Xyquil®XR Forte should be administered on an empty stomach with a glass of water. The modified-release tablets should be swallowed whole and should not be crushed, split or chewed to preserve the enteric coated core properties.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substances or to any of the excipients.
- Concomitant use with monoamine oxidase inhibitors (MAOIs) or use of **Xyquil®XR Forte** up to 14 days after cessation of MAOIs.
- Porphyria.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

This medicinal product may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine.
Use of this medicinal product is not recommended if a woman is concurrently using central nervous system (CNS) depressants including alcohol.
This medicinal product has anticholinergic properties and, therefore, should be used with caution in patients with: increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction as the anticholinergic effects of this medicinal product may worsen these conditions.

This medicinal product should also be used with caution in patients with asthma or other breathing disorders, such as chronic bronchitis and pulmonary emphysema. It has been demonstrated that antihistamines reduce the volume of bronchial secretions and increase their viscosity, thereby making bronchial expectoration more difficult. This may result in respiratory obstruction, which may worsen these conditions. As such, care should be taken in these patients.
This medicinal product should be used with caution in patients with hepatic or renal impairment. No data are available. However, the metabolism of doxylamine and pyridoxine may theoretically be reduced in the presence of hepatic impairment. Also, there could be a theoretical metabolite accumulation in the presence of renal impairment.
Xyquil® XR Forte contains pyridoxine hydrochloride, a vitamin B6 analog, therefore additional levels from diet and vitamin B6 supplements should be assessed.
The combination Doxylamine Succinate + Pyridoxine HCl has not been studied in cases of hyperemesis gravidarum; therefore, caution should be taken. These patients should be treated by a specialist. Early treatment of symptoms related to morning sickness typically in pregnancy, is recommended to prevent progression to hyperemesis gravidarum.
Photosensitivity reactions: Although not noted with doxylamine, an increased sensitivity of the skin to sunlight, with photodermatitis, has been observed with some antihistamines; thus, sunbathing should be avoided during treatment.
Ototoxic medications: Sedating antihistamines of the ethanolamine class, like doxylamine, could mask the warning signs of damage caused by ototoxic drugs such as antibacterial aminoglycosides, carboplatin, cisplatin, chloroquine and erythromycin, among others.
Care should be taken in epileptic patients as antihistamines have occasionally been associated with paradoxical hyperexcitability reactions, even at therapeutic doses.
Due to decreased sweating caused by anticholinergic effects, antihistamines may aggravate symptoms of dehydration and heat stroke.
Special precautions should be adopted in patients with long QT syndrome, as several antihistamines may prolong the mentioned QT interval, although this effect has not been observed specifically with doxylamine at therapeutic dose.
The suitability of treating patients with hypokalemia or other electrolyte disturbances must be evaluated.
The risk of abuse and drug dependence of doxylamine is low. The occurrence of signs suggestive of abuse or dependence should be carefully monitored, especially in patients with a history of drug use disorders.
There have been reports of false positive urine screening tests for methadone, opiates, and phencyclidine phosphate (PCP) with doxylamine succinate/pyridoxine hydrochloride use.

Interference with allergy skin testing: Antihistamines may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing.
Excipients: This medicinal product contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Known or theoretical interactions with antihistamines of the ethanolamine class:

- Anticholinergic agents (tricyclic antidepressants, MAOI, neuroleptics): may enhance toxicity due to the addition of their anticholinergic effects. Monoamine oxidase inhibitors (MAOIs) prolong and intensify the anticholinergic effects of antihistamines and concomitant treatment with MAOIs or use of Doxylamine Succinate + Pyridoxine HCl up to 14 days after cessation of MAOIs is contraindicated.
- Sedatives (barbiturates, benzodiazepines, antipsychotic agents, opioid analgesics): may enhance the hypnotic action.
- Concurrent use with central nervous system (CNS) depressants including alcohol, hypnotic sedatives and tranquilizers is not recommended. The combination may result in severe drowsiness.
- Antihypertensive drugs with sedative effect on the CNS (especially alpha-methyldopa) because they may enhance the sedative effect when administered with antihistamines.
- Alcohol: enhanced toxicity, with altered intellectual and psychomotor capacity, has been reported in some studies. The mechanism has not been established.
- Sodium oxybate as a not recommended combination with doxylamine due to its important central depressant effect.
- Ototoxic medications: Sedating antihistamines of the ethanolamine class, like doxylamine, could mask the warning signs of damage caused by ototoxic drugs such as antibacterial aminoglycosides.
- Photosensitizing medications: The concurrent use of antihistamines with other photosensitizing medications such as amiodarone, quinidine, imipramine, doxepin, amitriptyline, griseofulvin, chlorpheniramine, piroxicam, furosemide, captopril among others, may cause additive photosensitizing effects.
- Since several antihistaminic agents may prolong the QT interval, although this effect has not been observed with doxylamine at therapeutic dose, concomitant use of drugs that prolong the interval should be avoided (e.g. antiarrhythmic drugs, certain antibiotics, certain drugs for malaria, certain

antihistaminic drugs, certain antilipidemic drugs or certain neuroleptic agents).

- Due to the known metabolism pathway of doxylamine and lack of data on interactions, concomitant use with potent inhibitors of CYP2D6 (e.g. fluoxetine, terbinafine), CYP1A2 (e.g. fluvoxamine, cimetidine) and CYP2C9 (e.g. gemfibrozil, amiodarone) should be avoided as a precautionary measure.
- Concomitant use of drugs that cause electrolyte disturbances such as hypokalaemia or hypomagnesaemia (e.g. some diuretics) should be avoided.

The anticholinergic effects of doxylamine, a component of this medicinal product, could lead to false negatives in dermal hypersensitivity tests with antigen extracts. It is recommended to discontinue the treatment several days before starting the test.

Known or theoretical interactions with pyridoxine:

- Reduce the effect of levodopa although it does not occur if co-administered with an inhibitor of dopa decarboxylase.
- It has been described a reduction in plasma levels of some antiepileptics such as phenobarbital and phenytoin.
- Some medications such as hydroxyzine, isoniazid or penicillamine may interfere with pyridoxine and may increase requirements for vitamin B6.

Food: A food-effect study has demonstrated that the delay in the onset of action of this medicinal product may be further delayed, and a reduction in absorption may occur when tablets are taken with food. Therefore, this medicinal product should be taken on an empty stomach with a glass of water.

Interference with urine screen for Methadone, Opiates and PCP: False positive urine drug screens for methadone, opiates, and PCP can occur with doxylamine succinate/pyridoxine hydrochloride use. Confirmatory tests, such as Gas Chromatography Mass Spectrometry (GC-MS), should be used to confirm the identity of the substance in the event of a positive immunoassay result.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: No human data available.

Pregnancy: This medicinal product is intended for use in pregnant women.

Breast-feeding: Pyridoxine hydrochloride/metabolites are excreted into human milk. There have been no reports of adverse reactions in infants presumably exposed to pyridoxine hydrochloride through human milk. As newborn infants may be more sensitive to the effects of the antihistamines and to paradoxical irritability and excitation, a risk to newborns/infants cannot be excluded. This medicinal product is not recommended during lactation. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from this

medicinal product therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Doxylamine Succinate + Pyridoxine HCl has a moderate to major influence on the ability to drive and use machines.

Doxylamine Succinate + Pyridoxine HCl may cause somnolence and blurred vision, especially during the first few days of treatment. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using Doxylamine Succinate + Pyridoxine HCl until cleared to do so by their healthcare provider.

4.8. UNDESIRABLE EFFECTS:

The adverse reactions ranked under headings of system organ class and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Rare: Haemolytic anaemia
Immune system disorders:
Not known: Hypersensitivity
Psychiatric disorders:
Uncommon: Confusional state
Rare: Agitation
Not known: Anxiety, disorientation, insomnia, irritability, nightmares
Nervous system disorders:
Very Common: Somnolence
Common: Dizziness
Rare: Tremor, seizure
Not known: Headache, migraines, paraesthesia, psychomotor hyperactivity
Eye disorders:
Uncommon: Diplopia, glaucoma
Not known: Vision blurred, visual impairment
Ear and labyrinth disorders:
Uncommon: Tinnitus
Not known: Vertigo
Cardiac disorders:
Not known: Palpitation, tachycardia
Vascular disorders:
Uncommon: Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders:
Common: Increased bronchial secretion

Not known: Dyspnoea
Gastrointestinal disorders:
Common: Dry mouth
Uncommon: Nausea, vomiting
Not known: Abdominal distention, abdominal pain, constipation, diarrhoea
Skin and subcutaneous tissues disorders:
Uncommon: Photosensitivity reaction
Not known: Hyperhidrosis, pruritus, rash, rash maculo-papular
Renal and urinary disorders:
Not known: Dysuria, urinary retention
General disorders and administration site conditions:
Common: Fatigue
Uncommon: Asthenia, oedema peripheral
Not known: Chest discomfort, malaise

4.9. OVERDOSE:

Doxylamine Succinate + Pyridoxine HCl a modified-release formulation; therefore, signs and symptoms may not be apparent immediately.

Symptoms: Signs and symptoms of overdosage may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia. At toxic doses, doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis, acute renal failure, arrythmias, torsade de pointe and death.

Management: In the event of an overdose, treatment consists of activated charcoal, whole bowel irrigation and symptomatic treatment. Management should be in accordance with established treatment guidelines.

Paediatric population: Fatalities have been reported from doxylamine overdose in children. The overdose cases have been characterized by coma, grand mal seizures and cardiorespiratory arrest. Children appear to be at a high risk for cardiorespiratory arrest. A toxic dose for children of more than 1.8mg/kg has been reported. A 3-year-old child died 18 hours after ingesting 1,000mg doxylamine succinate. However, there is no correlation between the amount of doxylamine ingested, the doxylamine plasma level and clinical symptomatology.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antihistamines for systemic use.

ATC code: R06AA59

Mechanism of action: **Xyquil® XR Forte** provides the action of two unrelated compounds. Doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B_6) provide anti-nauseant and antiemetic activity. Doxylamine succinate is an ethanolamine derivative, a first-generation

antihistamine that is competitively, reversibly and non-specifically blocking H1-receptors. It is also a non-specific antagonist that blocks other receptors, such as central or peripheral muscarinic receptors. The antiemetic effect of doxylamine is also associated with the blocking of the central cholinergic and H1 receptors, although the mechanism of action is unknown. Pyridoxine hydrochloride, a water-soluble vitamin, is converted to pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate. Although pyridoxal 5'-phosphate is the main active antiemetic metabolite, the other metabolites also contribute to the biological activity. The mechanism of action of the combination of doxylamine succinate and pyridoxine hydrochloride to treat nausea and vomiting of pregnancy has not been established.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption: Doxylamine and pyridoxine are absorbed in the gastrointestinal tract, mainly in the jejunum. When formulated as a modified-release tablet, after single dose administration, the median peak plasma concentration of doxylamine and pyridoxine was achieved within 4.5 and 0.5 hours, respectively.

Distribution: Doxylamine is low protein binding (unbound fraction of 28.7% in rat), highly permeable, and is not a substrate of P-glycoprotein, leading to a wide distribution into tissues. Doxylamine crosses the blood-brain barrier and has a high affinity for H1 receptors. Pyridoxine is highly protein bound, primarily to albumin. Its metabolites, pyridoxal and pyridoxal 5'-phosphate are partially and almost completely bound to albumin in plasma, respectively. Its main active metabolite pyridoxal 5'-phosphate (PLP) accounts for at least 60% of circulating vitamin B_6 concentrations.

Biotransformation: Doxylamine is biotransformed in the liver primarily by the cytochrome P450 enzymes CYP2D6, CYP1A2, and CYP2C9, to its principal metabolites N-desmethyl-doxylamine and N,N-didesmethyldoxylamine. Pyridoxine is a prodrug primarily metabolized in the liver, with a high first pass effect. The metabolic scheme for pyridoxine is complex, with formation of primary and secondary metabolites along with interconversion back to pyridoxine. Pyridoxine and its metabolites, pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate contribute to biologic activity.

Elimination: The principal metabolites of doxylamine, N-desmethyl-doxylamine and N,N didesmethyldoxylamine, are excreted by the kidney. Renal elimination is also the main pathway of excretion for the derivatives of pyridoxine metabolism (reported to be 74% of a 100mg intravenous dose of pyridoxine), mainly as the inactive form 4-pyridoxic acid. When formulated as a modified-release tablet, after single dose administration, the terminal elimination half-life of doxylamine and pyridoxine are 12.43 and 0.27 hours, respectively.

Hepatic Impairment: No pharmacokinetic studies have been conducted in hepatic impaired patients.

Renal Impairment: No pharmacokinetic studies have been conducted in renal impaired patients.

5.3. PRECLINICAL SAFETY DATA:

Non-clinical data reveal no special hazard for humans based on available data of repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproductive toxicity: In a reproductive toxicity study of a drug product containing equal concentrations of doxylamine succinate and pyridoxine hydrochloride in rats, maternal toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Developmental toxicity (including reduced prenatal viability and reduced foetal body weight per litter, reduced foetal ossification in anterior distal limbs) only occurred in the presence of maternal toxicity (at doses from 60 times the maximum human recommended based on mg/m^2). No teratogenic effects are reported.

6. PHARMACEUTICAL PROPERTIES

6.1. LIST OF EXCIPIENTS:

- Microcrystalline Cellulose
- Magnesium trisilicate
- Croscarmellose Sodium
- Silicon Dioxide Fumed
- Magnesium Stearate
- Hypromellose
- Polyethylene Glycol
- Sheff coat
- Red iron oxide
- Sodium Lauryl Sulfate
- Sodium Bicarbonate
- Talcum Powder
- Titanium Dioxide
- Carnauba wax

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C and protect from heat and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/Alu Blister, pack size is 30's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

Innovator's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

126777

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

28th March, 2025

10. DATE OF REVISION OF THE TEXT

زائیکوئیل® ایکس آر فورٹ ٹیبلٹ

(ڈوکسیلامین سکسینیٹ + پائیری ڈوکسین ہائیڈروکلورائیڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔