SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NUSSIDEX®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active Ingredients

Dexchlorpheniramine maleate	1 mg
Pseudoephedrine (as hydrochloride)	25 mg

Excipients with known effect*:*

Lactose content: 208 mg per tablet.

Sodium content: 0.31-0.47 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral use.

White, round biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of the common cold and allergic rhinitis (hay fever).

4.2 Posology and method of administration

Adults

1-2 tablets, twice a day, after/with meals.

Children 6-12 Years of Age

1 tablet once a day ,after/with meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Children under 6 years of age.
- Patients with:
    - Cardiovascular disease including hypertension
    - Diabetes mellitus
    - Phaeochromocytoma
    - Hyperthyroidism
    - Closed angle glaucoma
    - Severe renal impairment
    - Risk of developing respiratory failure
- Should not be used concomitantly with:
    - Monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs. The concomitant use of pseudoephedrine and these products may cause a rise in blood pressure and/or hypertensive crisis.
    - Other sympathomimetic decongestants
    - Beta-blockers

4.4 Special warnings and precautions for use

Dexchlorpheniramine maleate

- Dexchlorpheniramine maleate may cause drowsiness and may add to the effects of alcohol. Drowsiness may continue the following day. Those affected should not drive or operate machinery; alcohol should be avoided.

- Dexchlorpheniramine maleate should be used with caution in patients with:
  - narrow-angle glaucoma
  - stenosing peptic ulcer
  - prostatic hypertrophy
  - bladder neck obstruction
  - pyloroduodenal obstruction
  - cardiovascular disease including hypertension
  - increased intraocular pressure
  - hyperthyroidism
  - use with caution in patients with renal or hepatic impairment
  - seizures

Dexchlorpheniramine maleate may cause photosensitivity in some patients.

Pediatric Use
Dexchlorpheniramine maleate is contraindicated in children under 6 years of age.
Children may experience paradoxical excitation with dexchlorpheniramine maleate. In children this may cause excitability.

Use in the Elderly
The elderly may experience paradoxical excitation with dexchlorpheniramine maleate. In patients over 60 years of age, antihistamines may cause dizziness, sedation and hypotension. Also they are more likely to have central nervous system (CNS) depressive side effects, including confusion.

Effect on laboratory tests
Antihistamines should be discontinued approximately 48 hours prior to skin testing procedures since these medicines may prevent or diminish otherwise positive reactions to dermal reactivity indicators.

Pseudoephedrine
Although pseudoephedrine has virtually no pressor effects in normotensive patients, this medicine should be used with caution in patients taking antihypertensive agents, tricyclic antidepressants or other sympathomimetic agents (such as appetite suppressants and amphetamine-like psychostimulants). The effects of a single dose on the blood pressure of these patients should be observed before recommending repeated or unsupervised treatment.

The physician or pharmacist should check that sympathomimetic containing preparations are not simultaneously administered by several routes i.e. orally and topically (nasal, aural and eye preparations) (see sections 4.3 and 4.5)

Patients with difficulty in urination and/or enlargement of the prostate should be advised to consult a physician before using this product.

Patients with thyroid disease who are receiving thyroid hormones should not take pseudoephedrine unless directed by a physician.
A variety of allergic skin reactions, with or without systemic features such as bronchospasm, angioedema have been reported following use of pseudoephedrine (see section 4.8).

Severe Skin reactions
Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of this medicine should be discontinued and appropriate measures taken if needed.

Ischaemic colitis
Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy
Cases of ischaemic optic neuropathy have been reported with pseudoephedrine. Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) / reversible cerebral vasoconstriction syndrome (RCVS) reported with sympathomimetic drugs, including pseudoephedrine. Symptoms reported include sudden onset of severe headache, nausea, vomiting, and visual disturbances. Most cases improved or resolved within a few days following appropriate treatment. Pseudoephedrine should be discontinued, and medical advice sought immediately if signs or symptoms of PRES/RCVS develop.

This product may act as a cerebral stimulant giving rise to hyperpyrexia, tremor and epileptiform convulsions. Care should be taken when used in epileptic patients.

If any of the following occur, this product should be stopped:
- Hallucinations
- Restlessness
- Sleep disturbances

Use with caution in occlusive vascular disease.

Effect on laboratory tests
Pseudoephedrine may induce positive results in certain anti-doping tests.

Sodium
Nussidex contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Drug Interactions
The following interactions with ***Dexchlorpheniramine*** have been noted:
- central nervous system (CNS) depressants (alcohol, sedatives, opioid analgesics, hypnotics) may cause an increase in sedative effects of Dexchlorpheniramine maleate
- concomitant administration with tricyclic antidepressants (TCAs) may result in additive antimuscarinic activity

- monoamine oxidase inhibitors (MAOIs) may prolong and intensify the anticholinergic and CNS depressive effects of some antihistamines and may cause a decrease in blood pressure
- oral anticoagulants may have their actions decreased by antihistamines.

The following interactions with ***Pseudoephedrine*** have been noted:
- MAOIs and/or RIMAs: Pseudoephedrine exerts its vasoconstricting properties by stimulating α-adrenergic receptors and displacing noradrenaline from neuronal storage sites. Since MAOIs impede the metabolism of sympathomimetic amines and increase the store of releasable noradrenaline in adrenergic nerve endings, MAOIs may potentiate the pressor effect of pseudoephedrine.

This medicine should not be given to patients treated with monoamine inhibitors or within 14 days of stopping treatment as there is an increased risk of hypertensive crisis.

- Moclobemide: risk of hypertensive crisis

- Sympathomimetic agents: Concomitant use of this medicine with tricyclic antidepressants (TCAs) or with sympathomimetic agents (such as appetite suppressants and amphetamine-like psychostimulants) may cause a rise in blood pressure.

- Anticholinergic drugs: The effects of anti-cholinergics e.g., some psychotropic drugs (such as tricyclic antidepressants) and atropine, may be potentiated by this product giving rise to tachycardia, mouth dryness, gastrointestinal disturbances, e.g., colic, urinary retention and headache.

- Antihypertensives: Pseudoephedrine may antagonise the hypotensive action of antihypertensive drugs which interfere with sympathetic activity including bretylium, betanidine, reserpine, guanethidine, debrisoquine, methyldopa, adrenergic neurone blockers - and beta- blockers (see sections 4.3 and 4.4).

- Because of its pseudoephedrine content, concomitant use of this medicine with oxytocin or cardiac glycosides may cause of a risk of hypertension or an increased risk of dysrhythmias, respectively.

- When used concurrently with ergot alkaloids (ergotamine & methysergide), this product can increase the risk of ergotism.

- Anaesthetic agents: Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

4.6 Fertility, Pregnancy and Lactation

Dexchlorpheniramine

Pregnancy

Safety during pregnancy has not been established. Dexchlorpheniramine maleate should be used during the first two trimesters of pregnancy only if clearly needed.
Dexchlorpheniramine maleate should not be used in the third trimester of pregnancy because newborn and premature infants may have severe reactions to antihistamines.
Dexchlorpheniramine maleate has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects of on the foetus having been observed.

Breastfeeding

Dexchlorpheniramine maleate is excreted in breast milk. Therefore caution should be exercised when administered to nursing mothers.

Pseudoephedrine
There are no adequate and well controlled clinical studies in pregnant or breast feeding women for the combination of pseudoephedrine.

Pregnancy
Although pseudoephedrine has been in widespread use for many years without apparent ill consequence, there are no specific data on its use during pregnancy. Caution should therefore be exercised by balancing the potential benefit of treatment to the mother against any possible hazards to the developing foetus.

Breast-feeding
This medicine should not be used during lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the nursing infant.

4.7 Effects on ability to drive and use machines

May cause drowsiness and may add to the effects of alcohol. Drowsiness may continue the following day. Those affected should not drive or operate machinery; alcohol should be avoided.
Patients should be cautioned about engaging in activities such as driving a car or operating machinery, until they have established their own response to the drug.

4.8 Undesirable Effects

Adverse reactions attributed to the antihistamine component (dexchlorpheniramine maleate)
Slight to moderate drowsiness is the most frequent side effect of dexchlorpheniramine maleate. Other reported reactions associated with antihistamine therapy in general include:

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat

Cardiovascular: Hypotension, hypertension, headache, palpitations, tachycardia, extrasystoles

Haematological: Haemolytic anaemia, hypoplastic anaemia, thrombocytopenia, agranulocytosis

Gastrointestinal: Epigastric distress, anorexia, nausea, vomiting, diarrhoea, constipation

Genitourinary: Urinary frequency, difficult urination, urinary hesitation and retention, early menses

Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paraesthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions, lassitude, depression, inability to concentrate, dilated pupils, hypereflexia, hyporeflexia, xerostomia, hallucinations, appetite stimulation, anxiety, facial dyskinesias and seizures

Respiratory: Thickening of bronchial secretions, tightness of chest, wheezing, nasal stuffiness

Adverser Reactions attributed to pseudoepehdrine component
Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with pseudoephedrine are listed below by System Organ Class (SOC).
The frequencies are defined according, to the following convention:
Very common ≥1/10

Common ≥1/100 and < 1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)
ADRs identified are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence cannot be estimated, frequency category is listed as 'Not known'.

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Immune System Disorders	Rare	Hypersensitivity (cross-sensitivity may occur with other sympathomimetics)
Psychiatric Disorders	Common	Insomnia Nervousness
	Rare	Hallucination
	Not known	Agitation Anxiety Delusion Euphoric mood Hallucination, visual Irritability Restlessness Sleep disorder
Nervous System Disorders	Very common	Headache
	Common	Dizziness
	Not known	Cerebrovascular accident Paraesthesia Posterior reversible encephalopathy syndrome (PRES) / Reversible cerebral vasoconstriction syndrome (RCVS) Psychomotor hyperactivity Somnolence Tremor
Eye Disorders	Not known	Ischaemic optic neuropathy
Cardiac Disorders	Not known	Arrhythmia Myocardial infarction/Myocardial ischaemia Palpitations Tachycardia
Vascular Disorders	Not known	Hypertension
Gastrointestinal Disorders	Common	Dry mouth Nausea
	Not known	Abdominal pain Diarrhoea Vomiting, Ischaemic colitis
Skin and Subcutaneous Tissue Disorders	Not known	Severe skin reactions, including acute generalised exanthematous pustulosis (AGEP) Angioedema Pruritus
	Rare	Rash
Renal and Urinary Disorders	Not known	Dysuria Urinary retention (in men - prostatic enlargement could have been an important predisposing factor)

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdosage

For Dexchlorpheniramine Maleate (Antihistamines)
Manifestations
Antihistamine overdosage effects may vary from central nervous system depression (apnoea, arrhythmias, cardiovascular collapse, cyanosis, diminished mental alertness, sedation) to stimulation (convulsions, hallucinations, insomnia or tremors) to death. Other signs and symptoms may be ataxia, blurred vision, dizziness, hypotension and tinnitus. Stimulation is particularly likely in children, as are atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing; gastrointestinal symptoms and hyperthermia).

Treatment
Dialysis is of little value in antihistamine poisoning. Treatment of the signs and symptoms of an over dosage are symptomatic and supportive. Consider standard measures to remove any unabsorbed medicine. There is no specific antidote. Measures to enhance excretion (urinary acidification, haemodialysis) are not recommended.

For Pseudoephedrine
Manifestations
Overdosage may result in:
Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia
Psychiatric disorders: CNS stimulation, insomnia; irritability, restlessness, anxiety, agitation; confusion, delirium, hallucinations, psychoses
Nervous system disorders: seizures, tremor, intracranial haemorrhage including intracerebral haemorrhage, drowsiness in children
Eye disorders: mydriasis
Cardiac disorders: palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias,
myocardial infarction
Vascular disorders: hypertension, hypertensive crisis
Gastrointestinal disorders: nausea, vomiting, ischaemic bowel infarction
Musculoskeletal and connective tissue disorders: rhabdomyolysis
Renal and urinary disorders: acute renal failure, difficulty in micturition

Treatment
Measures should be taken to maintain and support respiration and control convulsions. Catheterisation of the bladder may be necessary. If desired, the elimination of pseudoephedrine can be accelerated by acid diuresis or by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dexchlorpheniramine Maleate
ATC Code: R06AB02
Antihistamines for systemic use – substituted alkylamines.
Dexchlorpheniramine, the d-isomer of the racemic compound chlorpheniramine, is two times more active than chlorpheniramine. Dexchlorpheniramine does not prevent the release of histamine, but rather, competes with free histamine for binding at the H1-receptor sites, and competitively antagonizes the effects of histamine on H1-receptors in the GI tract, uterus, large

blood vessels, and bronchial muscle. Blockade of H1-receptors also suppresses the formation of oedema, flare, and pruritus that result from histaminic activity. Since dexchlorpheniramine binds to central and peripheral H1-receptors, sedative effects are likely to occur. H1-antagonists are structurally similar to anticholinergic agents and therefore possess the potential to exhibit anticholinergic properties of varying degrees. They also have antipruritic effects. Dexchlorpheniramine has high antihistaminic activity, moderate anticholinergic effects and minimal sedative effects. The medicine does not possess antiemetic properties.

Pseudoephedrine
ATC Code: R01BA02
Pseudoephedrine has direct and indirect sympathomimetic activity and is an effective upper respiratory tract decongestant.
Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation in systolic blood pressure and considerably less potent in causing stimulation of the central nervous system.

5.2 Pharmacokinetic Properties

Dexchlorpheniramine Maleate
The absorption, distribution, metabolism and elimination of dexchlorpheniramine have not been specifically described. However, since dexchlorpheniramine is the primary active isomer of the racemic compound chlorpheniramine, the pharmacokinetics of dexchlorpheniramine are likely to be similar to that of chlorpheniramine.
Dexchlorpheniramine is administered orally. H1-antagonists are generally well absorbed from the GI tract. The onset of action of immediate release formulations of chlorpheniramine is about 30-60 minutes. The Cmax of chlorpheniramine occurs in about 2 hours, the maximum therapeutic effect in about 6 hours, and the duration of action lasts between 4-8 hours. Protein binding is approximately 72%. Chlorpheniramine is widely distributed in body tissues and fluids, and it crosses the placenta and is excreted into breast milk.
The metabolism of chlorpheniramine is extensive and rapid, first occurring in the gastric mucosa and then on first-pass through the liver, which may be saturable. N-dealkylation produces several metabolites, which are excreted in the urine along with the parent compound. The half-life in healthy adults and children is 20-24 hours and 10-13 hours, respectively. Excretion rates are dependent on the pH of urine and urinary flow, with the rate decreasing as the pH rises and urinary flow decreases.

Pseudoephedrine
Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite.
Pseudoephedrine and its metabolite are excreted in the urine: 55% to 75% of a dose is excreted unchanged. The rate of urinary excretion of pseudoephedrine is accelerated when the urine is acidified. Conversely as the urine pH increases, the rate of urinary excretion is slowed.
In a limited study, three mothers nursing healthy infants were given an antihistamine-decongestant preparation containing 60 mg of pseudoephedrine and 2.5 mg of triprolidine. Milk concentrations of pseudoephedrine were higher than plasma levels in all three patients, with peak milk concentrations occurring at 1.0–1.5 hours. The investigators calculated that 1000 ml of milk produced during 24 hours would contain approximately 0.5%–0.7% of the maternal dose. However, following a single-blind, crossover study of a single dose of pseudoephedrine 60 mg vs. placebo conducted in 8 lactating mothers, and assuming maternal intake of 60 mg pseudoephedrine hydrochloride four times daily, the estimated infant dose of pseudoephedrine based on AUC and an estimated milk production rate of 150 ml/kg/day was 4.3% (95% CI, 3.2, 5.4%; range 2.2 to 6.7%) of the weight-adjusted maternal dose.

5.3 Preclinical safety data

Pseudoephedrine

Mutagenicity

The results of a wide range of tests indicate that pseudoephedrine does not post a mutagenic risk to man.

Carcinogenicity

There is insufficient information available to determine whether pseudoephedrine has carcinogenic potential.

Teratogenicity

Systemic administration of pseudoephedrine, up to 50 times the human daily dosage in rats and up to 35 times the human daily dosage in rabbits did not produce teratogenic effects.

Fertility

Systemic administration of pseudoephedrine to rats, up to 7 times the human daily dosage in females and 35 times the human daily dosage in males, did not impair fertility or alter foetal morphological development and survival.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Povidone
Talc
Magnesium stearate
Colloidal silicon dioxide
Hypromellose
Titanium dioxide
Macrogol/PEG 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a dry place, below 25°C.

6.5 Nature and Contents of Container

Available in blister packs of 20 or 30 tablets.
Not all pack sizes may be marketed**.**

6.6 Special Precautions for Disposal

Medicines should not be disposed of via wastewater or household waste. Ask a pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. LICENCE HOLDER AND MANUFACTURER

Licence holder & Manufacturer:

Teva Israel Ltd
124 Dvora Hanevi'a ST. Tel Aviv 6944020, Israel

8. REGISTRATION NUMBER

057-17-21688

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