1. NAME OF THE MEDICINAL PRODUCT

NOVADEX NIGHT CAPLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Paracetamol ..... 500 mg

Diphenhydramine Hydrochloride .....25 mg

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Blue, oblong biconvex caplet.

4. Clinical particulars

4.1 Therapeutic indications

- For the short term treatment of bedtime symptoms of pain, for example arising from colds and flu, arthritis, rheumatic and muscle pain, neuralgia, backache, toothache, headache, migraine and period pain which is causing difficulty in getting to sleep.
- Relief of fever.

4.2 Posology and method ofadministration

Posology

Adults (including the elderly) and adolescents 16 years and over:
2 caplets to be taken 20 minutes before bedtime. Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 4000 mg (including this product) in any 24 hour period. Allow at least four hours between taking any paracetamol-containing product and this product.
Maximum daily dose of Novadex Night Caplet:
Two caplets (1000mg paracetamol, 50mg diphenhydramine) in 24 hours.

Adolescents 12 to 15 years:
1 caplet to be taken 20 minutes before bedtime. Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 3000 mg (including this product) in any 24 hour period. Allow at least four to six hours between taking any paracetamol-containing product and this product.
Maximum daily dose of Novadex Night Caplet:
One caplet (500mg paracetamol, 25mg diphenhydramine) in 24 hours.

Do not use in children under 12 years of age.

Should not be used with other anti-histamine containing preparations, including those used on the skin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

For adults, paracetamol should not be taken for more than a few days at a time except on medical advice.

For children, paracetamol should not be taken for more than 48 hours except on medical advice.

Do not exceed the stated dose.

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

Keep out of sight and reach of children.

Method of administration
Take with water or other fluid only at bedtime.

4.3 Contraindications
Not for use in children 12 years of age and younger.

Hypersensitivity to paracetamol, diphenhydramine hydrochloride or to any of the excipients.

Diphenhydramine is contraindicated for use in patients with:
- Narrow-angle glaucoma
- Stenosing peptic ulcer
- Symptomatic prostatic hypertrophy
- Bladder neck obstruction
- Pyloroduodenal obstruction

Diphenhydramine is contraindicated for use in:
- Newborns or premature infants
- Lactating women
- Patients taking monoamine oxidase inhibitors (MAOIs)

Refer to "Section 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION" for additional information.

4.4 Special warnings and precautions for use
Contains paracetamol. Do not use with any other paracetamol- containing products. The concomitant use with other products containing paracetamol may lead to an overdose.

Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

Paracetamol and diphenhydramine hydrochloride should be used with care in patients with:
- Impaired hepatic function
- Impaired renal function

Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

Avoid use with other antihistamine-containing preparations, including topical antihistamines and other cough and cold medicines.

Avoid concurrent use with alcohol, as diphenhydramine may increase the sedative effects of alcohol. Therefore, alcohol should be avoided (see Section 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Avoid use in elderly patients with confusion. Use with caution in the elderly, who are more likely to experience adverse effects.

Medical advice should be sought before taking in patients with:
- Hepatic or renal impairment. Underlying liver disease increases the risk of paracetamol-related liver damage.
- Glutathione depleted states as the use of paracetamol may increase metabolic acidosis.

- Concurrent use of drugs which cause sedation such as tranquillizers, hypnotics and anxiolytics as diphenhydramine may cause an increase in sedative effects (see Section 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Caution should be exercised in patients with epilepsy or seizure disorders, myasthenia gravis, prostatic hypertrophy, urinary retention, asthma, bronchitis and chronic obstructive pulmonary disease (COPD).

Diphenhydramine hydrochloride may cause drowsiness and may increase the effects of alcohol. Drowsiness may continue the following day. Those affected should not drive or operate machinery; alcohol should be avoided.

Do not take for more than 3 days without consulting a doctor. If symptoms persist, medical advice must be sought.

Use with caution with:
- Patients with epilepsy or seizure disorders, myasthenia gravis, narrow-angle glaucoma, prostatic hypertrophy, urinary retention, asthma, bronchitis and chronic obstructive pulmonary disease (COPD), moderate to severe hepatic impairment and moderate to severe renal impairment
- Monoamine oxidase inhibitors (MAOIs) or within 2 weeks of stopping an MAOI
- Drugs with antimuscarinic properties e.g. atropine, tricyclics antidepressants

Refer to "Interaction with other medicines and other forms of interaction" for additional information.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol.

In patients with glutathione depleted states such as sepsis, the use of paracetamol may increase the risk of metabolic acidosis.

If symptoms persist, medical advice must be sought.

Keep out of sight and reach of children.

<u>Use in hepatic impairment</u>
Paracetamol and diphenhydramine hydrochloride should be used with care in patients with:
- Impaired hepatic function

<u>Use in renal impairment</u>
Paracetamol and diphenhydramine hydrochloride should be used with care in patients with
- Impaired renal function

<u>Paediatric population</u>
Children may experience paradoxical excitation with diphenhydramine (see Section 4.3 CONTRAINDICATIONS")

<u>Use in the elderly</u>
The elderly may experience paradoxical excitation with diphenhydramine. The elderly are more likely to have central nervous system (CNS) depressive side effects, including confusion (see Section 4.3 "CONTRAINDICATIONS"). Should not be taken by elderly patients with confusion and paradoxical excitation in the elderly (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

<u>Effects on laboratory tests</u>
No data available.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions with paracetamol have been noted:
- The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding. Anticoagulant dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- Paracetamol absorption is increased by substances that increase gastric emptying, eg metoclopramide
- Paracetamol absorption is decreased by substances that decrease gastric emptying, eg propantheline, antidepressants with anticholinergic properties and narcotic analgesics
- Paracetamol may increase chloramphenicol concentrations
- The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents
- Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid
- Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol

The following interactions with diphenhydramine hydrochloride have been noted:
- Central nervous system (CNS) depressants (alcohol, sedatives, opioid analgesics, hypnotics) – may cause an increase in sedation effects
- Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) – may prolong and intensify the anticholinergic and CNS depressive effects
- Diphenhydramine is an inhibitor of the cytochrome p450 isoenzyme CYP2D6. Therefore, there may be a potential for interaction with drugs that are primarily metabolised by CYP2D6, such as metoprolol and venlafaxine.
- Diphenhydramine may potentiate the sedative effects of alcohol and other CNS depressants (e.g. codeine, tranquillizers, hypnotics and anxiolytics) and other antihistamines (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- As diphenhydramine has some anticholinergic activity, the effects of some anticholinergic drugs may be potentiated. This may result in tachycardia, dry mouth, blurred vision, gastrointestinal disturbances, urinary retention and headaches (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Avoid use with other antihistamine-containing preparations including topical preparations and cough and cold medicines.

4.6 Pregnancy and Lactation

Pregnancy (Category A)
This product should not be used during pregnancy without medical advice.

Both paracetamol and diphenhydramine have 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 on the foetus having been observed.

Use of sedating antihistamines during the third trimester may result in reactions in the newborn or premature neonates.

Breastfeeding
Novadex Night should not be used whilst breastfeeding without medical advice.
Paracetamol is excreted in small amounts (< 0.2%) in breast milk. Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the breastfed infant.

Diphenhydramine is excreted in breast milk. Therefore it is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.

Fertility
No data on the effect on fertility are available.

4.7 Effects on ability to drive and use machines
Novadex Night may cause drowsiness, dizziness, blurred vision, cognitive and psychomotor impairment which can seriously affect the patient's ability to drive or operate machinery. If affected, do not drive or operate machinery.

4.8 Undesirable effects
Paracetamol
Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol, if left untreated, can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency.

As the adverse reactions identified from post-marketing use are reported voluntarily from a population of uncertain size, the frequency is not known but likely to be very rare.

Table 1: Paracetamol post marketing data

Body System	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopaenia
Immune System disorders	Anaphylaxis. Cutaneous hypersensitivity reactions including,
	among others, skin rashes, angiodema, and Stevens Johnson syndrome and Toxic Epidermal Necrolysis.
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs.
Hepatobiliary disorders	Hepatic dysfunction

Diphenhydramine
Central nervous system (CNS) effects
CNS depressive effects of diphenhydramine hydrochloride include sedation and impaired performance (impaired driving performance, poor work performance, incoordination, reduced motor skills and impaired information processing). Performance may be impaired in the absence of sedation and may persist the morning after a night-time dose.
CNS stimulatory effects of diphenhydramine may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.
High doses of diphenhydramine may cause nervousness, tremor, insomnia, agitation and irritability.
Anticholinergic effects
Side effects of diphenhydramine associated with cholinergic blockage include dryness of the eyes, mouth and nose, blurred vision, urinary hesitancy and retention, constipation and tachycardia.
Adverse reactions that have been observed in clinical trials and which are considered to be common or very common are listed below. The frequency of other adverse reactions identified during post-marketing use is not known but these reactions are likely to be uncommon or rare.

Table 2: Diphenhydramine post marketing data

Body System	**Undesirable Effect**
General disorders and administration site conditions	Common: Fatigue (1/10 – 1/100)
Immune system disorders	Not known: Hypersensitivity reaction including rash, urticaria, dyspnoea and angioedema

disorders	Not known: Confusion, paradoxical excitation (eg increased energy, restlessness, nervousness) The elderly are more prone to confusion and paradoxical excitation.
Nervous system disorders	Common: Sedation, drowsiness, (1/10 – 1/100) disturbance in attention, unsteadiness, dizziness Not known: Convulsions, headache, paraesthesia, dyskinesias
Eye disorders	Not known: Blurred vision
Cardiac disorders	Not known: Tachycardia, palpitations
Respiratory, thoracic & mediastinal disorders	Not known: Thickening of bronchial secretions
Gastrointestinal disorders	Common: Dry mouth (1/10 – 1/100) Not known: Gastrointestinal disturbance including nausea, vomiting
Musculoskeletal and connective tissue disorders	Not known: Muscle twitching
Renal and urinary disorders	Not known: Urinary difficulty, urinary retention

* These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

4.9 Overdose

If an overdose is taken or suspected, immediately seek medical treatment even if you feel well because of the risk of delayed, serious liver damage.

Paracetamol overdose may cause liver failure which can lead to liver transplant or death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

Diphenhydramine overdose is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include mydriasis, fever, flushing, agitation, tremor, dystonic reactions, hallucinations and ECG changes. Large overdose may cause rhabdomyolysis, convulsions, delirium, toxic psychosis, arrhythmias, coma and cardiovascular collapse.

Treatment

Paracetamol

Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present. Administration of N-acetylcysteine may be required.

Diphenhydramine

Treatment should be supportive and directed towards specific symptoms. Convulsions and marked CNS stimulation should be treated with parenteral diazepam.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, Anilides
ATC code: N02B E01

Paracetamol

Paracetamol is a p-aminophenol derivative that exhibits analgesic and antipyretic activity. It does not possess anti-inflammatory activity. Paracetamol is thought to produce analgesia through a central inhibition of prostaglandin synthesis.
The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract. Paracetamol is, therefore, particularly suitable for patients with a history of disease or on concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or the elderly).

Diphenhydramine hydrochloride
Diphenhydramine hydrochloride competes with histamine at central and peripheral histamine$_1$-receptor sites, preventing the histamine-receptor interaction and subsequent mediator release.
Diphenhydramine is a highly lipophilic molecule that readily crosses the blood-brain barrier.
Diphenhydramine is highly selective for histamine$_1$-receptors but has little effect on histamine$_2$ or histamine$_3$ receptors. Diphenhydramine also activates 5-hydroxytryptamine (serotonin) and α-adrenergic receptors and blocks cholinergic receptors.
Diphenhydramine is effective in reducing sleep onset (ie time to fall asleep) and increasing the depth and quality of sleep.

5.2 Pharmacokinetic properties

Paracetamol
Absorption
Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral administration.
Distribution
Paracetamol is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses.
Biotransformation
Paracetamol is metabolised extensively in the liver.
The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage (more than 150 mg/kg or 10 g total paracetamol ingested) and if left untreated can cause irreversible liver damage.
Elimination
The elimination half-life varies from about 1 to 3 hours. Paracetamol is excreted in the urine mainly as inactive glucuronide and sulfate conjugates. Less than 5% is excreted unchanged.
Paediatric population
Paracetamol is metabolised differently by premature infants, newborns, infants and young children compared to adults, the sulfate conjugate being predominant.

Diphenhydramine hydrochloride
Absorption
Diphenhydramine hydrochloride is well absorbed from the gastro-intestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations are achieved about 1 to 4 hours after oral administration. The sedative effect also appears to be maximal within 1-3 hours after administration of a single dose. It is positively correlated with the plasma drug concentration.
Distribution
Diphenhydramine is widely distributed throughout the body, including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly (approx 80-85%) bound to plasma proteins.
Biotransformation
Metabolism is extensive, mainly in the liver. Multiple cytochrome p450 enzymes contribute to the metabolism of diphenhydramine, including CYP2D6. The drug is metabolised principally to diphenylmetoxyacetic acid and is also dealkylated. It undergoes first-pass metabolism in the liver and only

about 40-60% of an oral dose reaches systematic circulation as unchanged diphenhydramine. The metabolites are conjugated with glycine and glutamine and excreted in urine.

Elimination

Diphenhydramine is excreted mainly in the urine as metabolites; little (about 1%) is excreted as unchanged substance. The elimination half-life has been reported to range from 2.4 to 9.3 hours in healthy adults. The terminal elimination half-life is prolonged in liver cirrhosis.

5.3 Preclinical safety data

General toxicity

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Povidone K.30, Methyl Hydroxybenzoate, Talc, Magnesium Stearate, Indigo Carmine (FD & C Blue No.2), Deionised Water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

Protect from moisture and keep out of reach of children.

6.5 Nature and contents of container

Packs of 20 containing two blisters of 10 caplets each.

6.6 Special precautions for disposal

No special requirements.

7 APPLICANT/MANUFACTURER

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