SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diconal 10 mg + 30 mg Tablets.
Dipipanone/Cyclizine 10 mg/30 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of Dipipanone Hydrochloride and 30 mg of Cyclizine Hydrochloride

Excipient with known effect:
Lactose: 91.666 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet coloured deep pink, scored and coded 'F3A'

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diconal Tablets are indicated for the management of moderate to severe pain in medical and surgical conditions in which morphine may be indicated.

Cyclizine is effective in preventing nausea and vomiting associated with the administration of narcotic analgesics.

4.2 Posology and method of administration

Posology:

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with dipipanone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Adults:

The initial dose in all conditions is one tablet every 6 hours. It is unwise to exceed this dose in view of the difficulty in accurately predicting the initial central effects of dipipanone.

Should this dose fail to provide adequate analgesia, as in severe intractable pain or when other potent opioids have been used, it may be increased by half a tablet every six hours.

It is seldom necessary to exceed a dose of 30 mg dipipanone given 6-hourly (i.e. 12 tablets in 24 hours).

Elderly:
There is no specific information on the use of Diconal in elderly patients. In common with opioid drugs, Diconal may be expected to cause confusion in this age group, and careful monitoring is advised (see section 4.4).

Paediatric population:
There is no specific information on the use of Diconal in children. Diconal is very rarely indicated in children and dosage guidelines cannot be stated.

Method of administration:
Oral

4.3 Contraindications

Hypersensitive to active substance or to any of the excipients listed in section 6.1.

Patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.

Patients with obstructive airway disease, during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.

Head injury and raised intracranial pressure.

Acute alcohol intoxication. The anti-emetic properties of cyclizine may increase the toxicity of alcohol.

Individuals receiving monoamine oxidase inhibitors, or within 14 days of stopping such treatment.

Patients with ulcerative colitis since in common with other narcotic analgesics it may precipitate toxic dilatation or spasm of the colon.

Patients with paralytic ileus and delayed gastric emptying.

Patients with spasm of the biliary or renal tract, particularly immediately after operative interventions on the biliary tract.

Pre-operative period or during the first 24 hours post operatively.
Patients with severe hepatic impairment as it may precipitate hepatic encephalopathy or coma.

Severe renal impairment. Diconal, in common with all narcotic analgesics, may precipitate coma or severe and prolonged respiratory depression.

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over the- counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with dipipanone.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Concomitant use of alcohol and Diconal tablets may increase the undesirable effects of Diconal tablets and should be avoided.

Diconal should be used with caution in the debilitated since they may be more sensitive to the respiratory depressant effects.

Diconal should be used with caution (including consideration of dose administered) in the presence of the following:

Convulsive disorders
Delirium tremens
Hypothyroidism
Adrenocortical insufficiency
Hypopituitarism;
Prostatic hypertrophy
Shock
Diabetes mellitus
Myasthenia gravis
Hypotension and hypovolaemia
Pancreatitis
Obstructive bowel disorders
Inflammatory bowel disorders
Diseases of the biliary tract (see section 4.3)
Impaired respiratory function (see section 4.3)
Urinary retention

Diconal should not be used where there is a possibility of paralytic ileus occurring (see section 4.3). Should paralytic ileus be suspected to occur during use, treatment should be discontinued immediately.

Diconal is metabolised in the liver and excreted along with its metabolites in the urine. Where not contraindicated in patients with impaired hepatic and/or renal function,

Diconal should be given at less than the usual recommended dose, and the patient's response used as a guide to further dosage requirements.

Cyclizine may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure. Diconal should therefore be used with caution in patients with severe heart failure.

Cyclizine should be avoided in patients with porphyria. Therefore use of Diconal should also be avoided in these patients.

Because cyclizine has anticholinergic activity it may precipitate incipient glaucoma. It should be used with caution and appropriate monitoring in patients with glaucoma.

Extreme caution should be exercised when administering Diconal to patients with phaeochromocytoma, since hypertension has been reported in association with other potent opioids.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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

4.5 Interaction with other medicinal products and other forms of interaction

The central nervous system depressant effects of Diconal may be increased by phenothiazine drugs, alcohol, sedatives, gabapentin, antihypertensives, barbiturates, hypnotics, neuroleptics, muscle relaxants and tricyclic antidepressants. Concurrent administration of some phenothiazines increases the respiratory depressant effects of narcotic analgesics and also produces hypotension.

Cyclizine enhances the soporific effect of pethidine.

The action of opioids may in turn affect the activities of other compounds, for example its gastrointestinal effects may delay absorption as with mexiletine or may be counteractive as with metoclopramide.

Monoamine oxidase inhibitors (MAOIs) may prolong and enhance the respiratory depressant effects of opioids. Opioids and MAOIs used together may cause fatal hypotension and coma (see section 4.3).

Cimetidine inhibits the metabolism of opioids.

Because of its anticholinergic activity, cyclizine may enhance the side effects of other anticholinergic agents.

Cyclizine may mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibacterials.

Analgesic effects of opioid drugs tend to be enhanced by co-administration of dexamphetamine and hydroxyzine

Opioids may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Propranolol has been reported to enhance the lethality of toxic doses of opioids in animals, although the significance of this finding is not known for man. Caution should be exercised when these drugs are administered concurrently.

In vitro data suggest that St. John's Wort (Hypericum perforatum) may induce cytochrome P450 3A4. There is a theoretical possibility therefore, that plasma levels of opioids may be decreased during concomitant administration and increased upon withdrawal of St. John's Wort.

Although there are no pharmacokinetic data available for concomitant use of ritonavir with opioids, ritonavir induces the hepatic enzymes responsible for the glucuronidation of opioids, and may possibly decrease plasma concentrations of opioids.

Interference with laboratory tests
Opioids can react with Folin-Ciocalteau reagent in the Lowry method of protein estimation.

Opioids can also interfere with the determination of urinary 17-ketosteroids due to chemical structure effects in the Zimmerman procedure.

4.6. Fertility, pregnancy and lactation

Pregnancy
There is no evidence on the safety of the combination in human pregnancy nor is there evidence from animal work that the constituents are free from hazard. However, limited data from epidemiological studies of cyclizine and morphine in human pregnancies have found no evidence of teratogenicity. In the absence of definitive human data with the combination, the use of Diconal in pregnancy is not advised.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding:
Cyclizine is excreted in human milk, however, the amount has not been quantified.

Opioids can significantly suppress lactation. Opioids are excreted in human milk, but the amount is generally considered to be less than 1% of any dose.

Administration to nursing women is not recommended as dipipanone may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility:
Effects of opioid exposure on sexual maturation of male rats, their reproductive capacity and the development of their progeny have been examined. Results indicated that exposure during adolescence led to pronounced inhibition of several indices of sexual maturation (e.g. hormone levels, reduced gonad weights), smaller litters and selective gender specific effects on endocrine function in the offspring.

A disruption in ovulation and amenorrhoea can occur in women given morphine.

4.7 Effects on ability to drive and use machines

In common with other opioids, dipipanone may produce orthostatic hypotension and drowsiness in ambulatory patients. Sedation of short duration has been reported in patients receiving intravenous cyclizine. The CNS depressant effects of Diconal may be enhanced by combination with other centrally acting agents (see Interaction with other medicaments and other forms of interactions).
This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine

However, you would not be committing an offence (called 'statutory defence') if:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, 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.

The following undesirable effects have been reported with a frequency of Not known.

Adverse reactions attributable to dipipanone include:

System Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Not known	Allergic reaction, anaphylactic reaction, anaphylactoid reaction.
Metabolism and nutrition disorders	Not known	Decreased appetite
Psychiatric disorders	Not known	Confusion, mood changes, euphoria, dysphoria, psychosis, restlessness, insomnia, agitation, hallucinations, drug dependence (see section 4.4), decreased libido.
Ear and labyrinth disorders	Not known	Vertigo
Nervous system disorders	Not known	Somnolence, sedation, raised intracranial pressure, involuntary muscle contractions, dizziness, convulsions, hypertonia, paraesthesia, syncope, coma, headache, myoclonus, taste perversion.
Eye disorders	Not known	Miosis, visual disturbance.
Cardiac disorders	Not known	Tachycardia, bradycardia,

		palpitations.
Vascular disorders	Not known	Facial flushing, hypotension, hypertension, circulatory failure, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression, respiratory failure, bronchospasm, pulmonary oedema, cough decreased.
Gastrointestinal disorders	Not known	Constipation, nausea, vomiting, abdominal pain, ileus, dyspepsia, dry mouth, exacerbation of pancreatitis.
Hepatobiliary disorders	Not known	Biliary pain, biliary spasm.
Skin and subcutaneous tissue disorders	Not known	Hyperhidrosis, urticaria, rash, pruritus.
Renal and urinary disorders	Not known	Ureteric spasm, urinary retention, dysuria.
Reproductive system and breast disorders	Not known	Amenorrhea, erectile dysfunction.
General disorders and administration site conditions	Uncommon Not known	Drug withdrawal syndrome Asthenia, malaise, peripheral oedema, drug tolerance, hypothermia.
Investigations	Not known	Increased hepatic enzymes.

Adverse reactions attributable to cyclizine include:

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Not known	Agranulocytosis, leucopenia, haemolytic anaemia, thrombocytopenia.
Immune system disorders	Not known	Hypersensitivity reactions, including anaphylaxis has occurred.
Metabolism and nutrition disorders	Not known	Decreased appetite
Psychiatric disorders	Not known	Disorientation, restlessness or agitation, nervousness, euphoria, insomnia and auditory and visual hallucinations have been reported, particularly when dosage recommendations have been exceeded.
Ear and labyrinth disorders	Not known	Tinnitus

Nervous system disorders	Not known	Effects on the central nervous system have been reported with cyclizine these include: somnolence, headache, dystonia, decreased consciousness, dyskinesia, extrapyramidal motor disturbances, restless leg syndrome, tremor, convulsions, dizziness, decreased consciousness, transient speech disorders, paraesthesia, generalised chorea, drowsiness, incoordination. There have been rare case reports of patients experiencing depressed levels of consciousness/loss of consciousness.
Eye disorders	Not known	Blurred vision, oculogyration.
Cardiac disorders	Not known	Tachycardia, palpitations, arrhythmias.
Vascular disorders	Not known	Hypertension, hypotension.
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm, apnoea, nasal dryness, dry throat.
Gastrointestinal disorders	Not known	Dryness of the mouth, nose and throat. Constipation, increased gastric reflux, nausea, vomiting, diarrhoea, stomach pain.
Hepatobiliary disorders	Not known	Hepatic dysfunction, including hepatitis due to hypersensitivity. Cholestatic jaundice, cholestatic hepatitis
Skin and subcutaneous tissue disorders	Not known	Urticaria, drug rash, angioedema allergic skin reactions, fixed drug eruption, photosensitivity.
Musculoskeletal and connective tissue disorders	Not known	Twitching, muscle spasms.
Renal and urinary disorders	Not known	Urinary retention.

General disorders and administration site conditions	Not known	Asthenia, malaise

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 (Website: www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:
The signs of overdosage with Diconal are those pathognomic of opioid poisoning i.e. respiratory depression, bradycardia, pin point pupils, hypotension, circulatory failure and deepening coma. Mydriasis may replace miosis as asphyxia intervenes. Opioid overdose can result in death.

Drowsiness, floppiness, miosis and apnoea are signs of opioid overdosage in children as are convulsions.

Rhabdomyolysis progressing to renal failure has been reported in opioid overdosage.

Signs and symptoms of acute toxicity from cyclizine arise from peripheral anticholinergic effects and effects on the central nervous system.

Peripheral anticholinergic symptoms include, dry mouth, nose and throat, blurred vision, tachycardia and urinary retention.

Central nervous system effects include drowsiness, dizziness, incoordination, ataxia, weakness, hyperexcitability, disorientation, impaired judgement, hallucinations, hyperkinesia, extrapyramidal motor disturbances, convulsions, hyperpyrexia and respiratory depression.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Management:
It is imperative to maintain and support respiration and circulation.

The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and restoration of spontaneous respiration. The literature should be consulted for details of appropriate dosage.

The use of a specific opioid antagonist in patients tolerant to dipipanone may produce withdrawal symptoms.

Convulsions should be controlled with parenteral anticonvulsant therapy.

Patients should be monitored closely for at least 48 hours in case of relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives.
ATC code: R06AE53

Mechanism of action:
The onset of analgesic action of dipipanone is approximately one hour and lasts for 4 to 6 hours.

Cyclizine is a histamine H1 receptor antagonist of the piperazine class which is characterised by a low incidence of drowsiness. It possesses anticholinergic and antiemetic properties. The exact mechanism by which cyclizine can prevent or suppress both nausea and vomiting from various causes is unknown. Cyclizine increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus. It may inhibit the part of the midbrain known collectively as the emetic centre. Cyclizine produces its anti-emetic effect within 2 hours and lasts for approximately 4 hours.

5.2 Pharmacokinetic properties

Absorption:
Dipipanone is absorbed from the gastrointestinal tract.

In healthy adult volunteers, the administration of a single oral dose of 50 mg cyclizine resulted in a peak plasma concentration of approximately 70 nanogram/ml occurring approximately 2 hours after drug administration.

Biotransformation:
Dipipanone is metabolised in the liver.

Elimination:
Dipipanone excreted in the urine and faeces, although data on the proportions of parent compound and metabolites so excreted are lacking.

The plasma elimination half-life was approximately 20 hours.

The N-demethylated derivative, norcyclizine, has been identified as a metabolite of cyclizine. Norcyclizine has little antihistaminic (H_1) activity compared with cyclizine and has a plasma elimination half life of approximately 20 hours. After a single oral dose of 50 mg cyclizine given to a single adult male volunteer, urine collected over the following 24 hours contained less than 1% of the total dose administered.

5.3 Preclinical safety data

A. Mutagenicity

Cyclizine was not mutagenic in an Ames test (at a dose level of 100 µg/plate), with or without metabolic activation.

No bacterial mutagenicity studies with dipipanone have been reported. A review of the literature with regards to opioids has indicated that morphine was negative in gene mutation assays in Drosophila melanogaster, but was positive in a mammalian spermatocyte test. The results of another study by the same authors has indicated that morphine causes chromosomal aberrations, in germ cells of male mice when given at dose levels of 10, 20, 40 or 60 mg/kg bodyweight for 3 consecutive days.

B. Carcinogenicity

No long term studies have been conducted in animals to determine whether cyclizine or dipipanone are potentially carcinogenic.

C. Teratogenicity

Some animal studies indicate that cyclizine may be teratogenic at dose levels up to 25 times the clinical dose level. In another study, cyclizine was negative at oral dose levels up to 65 mg/kg in rats and 75 mg/kg in rabbits. The relevance of these studies to the human situation is not known.

There is no data of relevance for dipipanone, however, morphine was shown not to be teratogenic in rats when dosed for up to 15 days at 70 mg/kg/day. Morphine given subcutaneously to mice at very high doses (200, 300 or 400 mg/kg/day) on days 8 or 9 of gestation, resulted in a few cases of exencephaly and axial skeletal fusions. The hypoxic effects of such high doses could account for the defects seen.

Lower doses of morphine (40, 4.0 or 0.4 mg/ml) given to mice as a continuous i.v. infusion (at a dose volume of 0.3 ml/kg) between days 7 and 10 of gestation, caused soft tissue and skeletal malformations as shown in previous studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, starches, dye (FD and C Red No. 3), gelatin, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25°C. Protect from light. Keep dry.

6.5 Nature and contents of container

PVC/aluminium foil blister packs containing 50 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm UK Limited
Dashwood House,
69 Old Broad Street, London,
EC2M 1QS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th September 2003

10 DATE OF REVISION OF THE TEXT

31/01/2024