

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dalmane 30mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules with a black cap and opaque grey body with 30 printed in red on both cap and body, containing 32,8 mg flurazepam monohydrochloride (equivalent to 30 mg flurazepam).

Each capsule contains 97.7 mg lactose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Dalmane capsules 30mg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of insomnia when it is severe, disabling or subjecting the individual to extreme distress. Dalmane is helpful in overcoming difficulties in getting to sleep and also in the problem of frequent nocturnal awakenings. Its properties make it particularly indicated where the total duration of sleep is less than adequate.

An underlying cause for insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

4.2 Posology and method of administration

Posology:

Adults - The dosage of Dalmane should be determined on an individual basis taking into account the severity of the insomnia and the patient's response to treatment. Dosage is important in determining the duration of effect and the occurrence of residual effects. The usual dose is 15 or 30 mg. 15mg is optimal for most patients and this will ensure a full night's sleep with minimal residual effects on waking. Patients with severe insomnia may require 30 mg (but no more than 60 mg), but residual effects on awakening, associated with an anxiolytic effect, are more frequent at this dose.

Elderly or debilitated patients - The elderly will be particularly susceptible to the adverse effects of Dalmane. The initial dose should not exceed 15 mg. If organic brain changes are present, the dosage of Dalmane should not exceed 15 mg.

Patients with hepatic and renal impairment – The initial dose is 15 mg and in general should not be exceeded.

Patients with chronic pulmonary insufficiency - In patients with chronic pulmonary insufficiency the dosage may need to be reduced.

Paediatric population - Dalmane is contra-indicated for use in children.

Duration of treatment - Treatment should, if possible, be on an intermittent basis.

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

Treatment should be as short as possible and should be started with the lowest recommended dose. The maximum dose should not be exceeded. Generally the duration of treatment varies from a few days to two weeks with a maximum of four weeks, including the tapering off process.

In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status. Long-term chronic use is not recommended.

Flurazepam is a long-acting benzodiazepine so the patient must be regularly checked to reduce the dosage or frequency of administration if necessary to prevent overdose due to accumulation.

Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced. Specialist help may be appropriate. Little is known regarding the efficacy or safety of benzodiazepines in long-term use.

Method of administration:

Dalmane capsules are for oral administration.

The product should be taken just before going to bed.
To be swallowed with water without chewing.

4.3 Contraindications

Dalmane is contraindicated in:

-Patients with known hypersensitivity to flurazepam, other benzodiazepines or to any of the excipients listed in section 6.1

- myasthenia gravis;
- severe pulmonary insufficiency;
- respiratory depression;
- phobic or obsessional states;
- chronic psychosis;
- sleep apnoea syndrome;
- severe hepatic insufficiency;
- spinal and cerebellar ataxia; and
- use in children.

4.4 Special warnings and precautions for use

Dalmane should not be used alone to treat depression or anxiety associated with depression, since suicide may be precipitated in such patients.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

Benzodiazepines are not recommended for the primary treatment of psychotic illness. In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Dalmane is not indicated in patients with spinal and cerebellar ataxia.

Elderly patients should be given a reduced dose (see section 4.2 Posology). Due to the myorelaxant effect there is a risk of falls and consequently fractures in the elderly.

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy and reduced doses should be given to patients with renal or hepatic disease.

Dalmane should not be given in acute intoxication with alcohol, sedative agents, hypnotic agents, analgesics or psychotropic agents (neuroleptic agents, antidepressants, lithium).

Dalmane is not indicated for children. If necessary for compelling reasons, benzodiazepines should be prescribed for children and adolescents after careful appraisal of the risk-benefit ratio only.

Concomitant use of Dalmane and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Dalmane with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Dalmane concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose

reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended 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 drug 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 symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. 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 treatment with Flurazepam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Drug withdrawal syndrome

Prior to starting treatment with Flurazepam, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with Flurazepam should also be put in place with the patient (asymptom management in end-of-life palliative care).

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 in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

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

Rebound Insomnia and Anxiety:

This is a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is gradually decreased.

Psychiatric and paradoxical reactions:

Abnormal psychological reactions to benzodiazepines have been reported. Rare behavioural effects include paradoxical aggressive outbursts, excitement, confusion, restlessness, agitation, irritability, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and the uncovering of depression with suicidal tendencies. Extreme caution should therefore be used in prescribing benzodiazepines to patients with personality disorders. If any of these reactions occur, use of the drug should be discontinued. These reactions may be quite severe and are more likely to occur in children and the elderly.

Amnesia:

Benzodiazepines may induce anterograde amnesia. The condition usually occurs

1-2 hours after ingesting the product and may last up to several hours. Therefore, to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours.

If the patient is awoken during the period of maximum drug activity, recall may be impaired.

Duration of treatment:

The duration of treatment should be as short as possible (see section 4.2 Posology) depending on the indication, but should not exceed 4 weeks, including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased.

Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Patients with rare hereditary problems of galactose intolerance, 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 benzodiazepines, including flurazepam, produce additive CNS depressant effects when co-administered with other CNS drugs such as barbiturates, antipsychotics, sedative/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, anaesthetics, antihypertensives and beta (receptor) blockers.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines. In case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence. The elderly require special supervision.

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Dalmane with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

When Dalmane is used in conjunction with anti-epileptic drugs, side-effects and toxicity may be more evident, particularly with hydantoins or barbiturates or combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment.

Concomitant intake with muscle relaxants may increase the relaxant effect of flurazepam.

Known inhibitors of hepatic enzymes, eg cimetidine, omeprazole and disulfuram, have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, eg rifampicin, may increase the clearance of benzodiazepines.

Concomitant intake with alcohol should be avoided. The sedative effect of Dalmane may be modified and enhanced in an unpredictable way if the product is used in combination with alcohol. This adversely affects the ability to drive or use machines.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There is no evidence as to drug safety in human pregnancy, nor is there evidence from animal work that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

Administration of benzodiazepines in the last trimester of pregnancy or during labour has been reported to produce irregularities in the foetal heart rate, and hypotonia, poor sucking and hypothermia and moderate respiratory depression in the neonate.

Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Breast-feeding

There is insufficient information on the excretion of flurazepam and/or metabolites in human milk. However, in common with other benzodiazepines, its passage into breast milk might be expected. The use of Dalmane in mothers who are breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

Patients should be advised that, like all medicaments of this type, Dalmane might modify patients' performance at skilled tasks (driving, operating machinery, etc.) to a varying degree depending upon dosage, administration, and sleep pattern and individual susceptibility. Patients should further be advised that alcohol may intensify any impairment, and should therefore be avoided during treatment.

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:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely.

4.8 Undesirable effects

Common adverse effects include somnolence during the day, emotional poverty, reduced alertness, confusional state, fatigue, headache, dizziness,

muscle weakness, ataxia and diplopia. These phenomena are dose-related and are likely to be uncommon with the recommended dosage; they occur predominantly at the start of therapy and usually disappear with repeated administration or after dose adjustment. The elderly are particularly sensitive to the effects of centrally depressant drugs.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: 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 ($<1/10,000$), Frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Frequency not known: blood disorders (e.g. thrombocytopenia, leukopenia, agranulocytosis, pancytopenia).

Immune system disorders:

Rare: Hypersensitivity (e.g. angioedema)

Psychiatric disorders:

Uncommon: Emotional poverty,

Frequency not known: Confusional state, hallucinations, dependence, withdrawal syndrome, rebound effect, depression, paradoxical drug reactions (e.g. anxiety, sleep disorders, insomnia, nightmares, restlessness, agitation, irritability, aggression, delusion, psychotic disorder, abnormal behaviour, emotional disturbances, suicide attempt, suicidal ideation).

Drug dependence (see section 4.4)

Nervous system disorders:

Common: Somnolence, reduced alertness, ataxia, dizziness, headache, dysgeusia

Frequency not known: Extraprymidal disorder, anterograde amnesia

Eye disorders:

Rare: Visual impairment (e.g. diplopia)

Ear and labyrinth disorders:

Rare: Vertigo

Vascular disorders:

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders:

Rare: Respiratory depression (particularly at night)

Gastrointestinal disorders:

Rare: Abdominal discomfort, nausea

Hepatobiliary disorders:

Very rare: Jaundice, hepatic enzyme increase

Skin and subcutaneous tissue disorders:

Rare: Skin reactions (e.g. rash)

Musculoskeletal and connective tissue disorders:

Common: Muscle weakness. Due to the myorelaxant effect there is a risk of falls and consequently fractures in the elderly.

Renal and urinary disorders:

Rare: Urinary retention

Reproductive system and breast disorders:

Rare: Libido disorder

General disorders and administration site conditions:

Uncommon: Fatigue

Drug dependence (see section 4.4)

General disorders and administration site conditions:

Drug withdrawal symptoms (see 4.4 Special warnings and precautions).

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of “rebound” phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

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 the 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

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

When taken alone in overdosage Dalmane presents few problems in management and should not present a threat to life unless combined with other CNS depressants (including alcohol).

Symptoms:

Special attention should be paid to respiratory and cardiovascular functions in intensive care. Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, dysarthria and lethargy; in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Management:

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents might have been taken.

Following overdose with oral benzodiazepines, vomiting should be induced if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

The value of dialysis has not been determined. Flumazenil is a specific IV antidote for use in emergency situations. Patients requiring such intervention should be monitored closely in hospital (see separate prescribing information).

If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine derivatives,

ATC code: N05CD01

Flurazepam is a psychotropic substance from the class of 1,4-benzodiazepines. Onset of sedative effects occurs within 30 minutes. Due to accumulation of the active metabolite N1-desalkyl-flurazepam peak response is not observed before night 2-3 of treatment.

Flurazepam binds to specific benzodiazepine receptors located on GABA-ergic neurones and potentiates the inhibitory actions of GABA-ergic neurones in the nervous system.

After prolonged flurazepam treatment, development of tolerance has been observed. Chronic benzodiazepine use leads to compensating changes in the central nervous system. GABAA receptors may become less responsive to the continuing acute effects of benzodiazepines, either as a result of adaption in the GABAA receptor itself, intracellular mechanisms, or changes in the neurotransmitter systems. Probably multiple adaptive mechanisms simultaneously co-exist.

An increase in intensity and incidence of CNS toxicity with age has been observed, especially at high doses. Therefore the initial dose of Dalmane in elderly should not exceed 15 mg (see section 4.2) The increased CNS toxicity in elderly seems to be the result of the combination of pharmacokinetic and pharmacodynamic factors.

Under the treatment with 15 and 30 mg flurazepam impairment of psychomotor and cognitive performance was observed in several investigations. Especially the driving ability is affected (see section 4.7) In elderly patients the effect is more pronounced.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Dalmane make it particularly indicated for patients whose total duration of sleep is less than adequate. The dosage of the drug is important in balancing the duration of effect with the occurrence of residual effects.

Absorption:

Flurazepam hydrochloride is rapidly and almost completely absorbed after oral administration. Maximum plasma concentrations were measured after 1 to 3 hours. The maximum plasma concentrations of the two pharmacologically active major metabolites N1-hydroxyethyl-flurazepam and N1-desalkyl flurazepam were observed after 1 to 4 hours and 0.5 to 96 hours, respectively. In most subjects, the N1-desalkyl-flurazepam concentration reached a plateau value after 1 to 24 hours. The maximum plasma concentration of N1-hydroxyethyl-flurazepam ranges between 6 and 28 ng/ml and of N1-desalkyl-flurazepam ranges between 5 and 40 ng/ml after a single oral dose.

Distribution:

Flurazepam undergoes considerable first-pass metabolism. The plasma protein binding is high for flurazepam (83%) and N1-desalkyl-flurazepam (96.5%) and lower for N1-hydroxyethyl-flurazepam (65%). Taking flurazepam hydrochloride over a period of 15 days the N1-desalkyl-flurazepam accumulated. The plasma concentrations were 7.5 times higher on the 15th day versus the 1st day.

The concentration of flurazepam and its metabolites is 2 times (for N1-hydroxyethyl-flurazepam), 7 times (for flurazepam) or 8 times (for N1-desalkyl-flurazepam) higher in cerebrospinal fluid compared to plasma. In animal models, flurazepam was eliminated from serum in biphasic fashion, consistent with two-compartment model and volume of distribution was between 2.65 and 5.5 l/kg.

Flurazepam and/or active metabolites cross the placental barrier in rodents. Human data are not available.

No information concerning secretion of flurazepam and metabolites in the breast milk are available. However in common with other benzodiazepines, its passage into breast milk might be expected.

Biotransformation:

The plasma half-life for flurazepam and N1-hydroxyethyl-flurazepam was 3.1 hours and 2.3 to 3.4 hours, respectively. For N1-desalkyl-flurazepam, the corresponding values were 19 to 133 hours. In elderly subjects (66 - 85 years) still higher values for N1-desalkyl-flurazepam were obtained (71-289 hours). The metabolites are further conjugated to glucuronides and / or sulfates for renal excretion

Elimination:

Flurazepam monohydrochloride and its metabolites are eliminated primarily by renal excretion (about 80%). The major urinary metabolite, N1-hydroxyethyl-flurazepam as glucuronide/sulphate conjugate accounts for 20-55% of an orally administered dose.

5.3 Preclinical safety data

Mutagenic and tumourigenic potential:

There is insufficient data available to evaluate the genotoxic potential of flurazepam. The limited studies performed to date showed no evidence of genotoxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

30mg capsules contain the following excipients: lactose, talc purified, magnesium stearate, black iron oxide E172, titanium dioxide E171 and yellow iron oxide E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Amber glass bottles and plastic adept containers - 5 years

PVDC blister packs - 3 years

Polythene bags in tins and small HDPE bottles - 2 years

White securitainers - 1 year

6.4 Special precautions for storage

Dalmane capsules should be stored in a dry place with a recommended maximum storage temperature of 25°C.

6.5 Nature and contents of container

PVDC blister packs, amber glass bottles, polythene bags in tins, plastic adept containers, white securitainers and small HDPE bottles containing 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Viatrix Products Limited,
Station Close,

Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/0126

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

15/08/2001

10 DATE OF REVISION OF THE TEXT

09/02/2026