SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dalmane 30 mg Hard Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 30 mg flurazepam as flurazepam monohydrochloride. Excipients: Lactose monohydrate 97.7 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

Capsules with opaque black cap and opaque grey body with 'ICN30' printed in red on both cap and body.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Insomnia
Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2. Posology and method of administration

Insomnia
Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering off process of four weeks.
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.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

Adults:
The usual dosage is 15-30mg before retiring. 15mg is optimal for most patients. Patients with severe insomnia may require 30mg but residual effects on awakening, associated with anxiolytic effects, are more frequent at this dose.

Older or debilitated patients:
Older patients will be particularly susceptible to the adverse effects of Dalmane. The initial dose should not exceed 15mg. If organic brain changes are present, the dosage of Dalmane should be reduced (see section 4.4).

Use in patients with hepatic and renal impairment:
The dosage should be reduced in patients with renal or hepatic impairment. Dalmane is contraindicated in patients with severe hepatic failure (see sections 4.3 and 4.4.).

Use in patients with chronic pulmonary insufficiency:
In patients with chronic pulmonary insufficiency the dosage may need to be reduced.

Children:
Not recommended.

Method of administration
Oral use.

The product should be taken just before going to bed. The patient should be checked regularly at the start of the treatment in order to decrease if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

4.3. Contraindications

- Patients with hypersensitivity to flurazepam, other benzodiazepines or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Severe respiratory insufficiency
- Severe pulmonary insufficiency
- Sleep apnoea syndrome
- Severe hepatic insufficiency
- Phobic or obsessional states
- Chronic psychosis

4.4. Special warnings and precautions for use

Risk from concomitant use of opioids:

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.

Concomitant use of benzodiazepines/benzodiazepine like products and opioids 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).

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.

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.
Tolerance
Some loss of efficacy to the hypnotic effects may develop after repeated use for a few weeks.

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

Dependence
Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. This is particularly so in patients with a history of alcoholism or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Symptoms such as depression, nervousness, extreme anxiety, tension, restlessness, confusion, mood changes, rebound insomnia, irritability, sweating, diarrhoea, headaches and muscle pain has been reported following abrupt cessation of treatment in patients receiving even normal therapeutic doses for short periods of time. In severe cases the following symptoms may occur; derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact and hallucinations or epileptic seizures. In rare instances, withdrawal following excessive dosages may produce confusional states, psychotic manifestations and convulsions. Abuse of benzodiazepines has been reported.

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 decreased gradually.

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 four weeks for insomnia, 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.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. 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.

Amnesia
Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also section 4.8 Undesirable Effects).

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

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 more likely to occur in children and older patients.

Specific patient groups
Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.

Older patients should be given a reduced dose (see section 4.2 Posology). Due to myorelaxant effect of Dalmane there is a risk of falls and consequently of hip fractures particularly for older patients when they get up at night.

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.

The dosage should be reduced in patients with organic brain changes.

4.5. Interaction with other medicinal products and other forms of interaction

Not recommended: Concomitant intake with alcohol
The sedative effect 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.

Take into account: Combination with CNS depressants
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 the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence. Older patients require special supervision.

Opioids:
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).

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

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.

4.6. Fertility, pregnancy and lactation

Pregnancy
Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbances in offspring exposed in utero. There is no evidence as to drug safety in human pregnancy or evidence from animal work that it is free from hazard. Therefore, Dalmane should not be used 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 high doses 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 for developing withdrawal symptoms in the postnatal period.

Breast-feeding
No data regarding the passage of flurazepam into the breast milk are available. However, in common with other benzodiazepines, its passage into breast milk might be expected. If possible, the use of Dalmane in mothers who are breast-feeding should be avoided.

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. Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect ability to drive or operate machinery to a varying degree depending upon dosage, administration, and sleep pattern and individual susceptibility. This applies in particular following insufficient duration of sleep. Patients should further be advised that alcohol may intensify any impairment, and should, therefore, be avoided during treatment.

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.

Older patients 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 disorder
Frequency not known: Blood disorders (e.g. thrombocytopenia, leucopenia, agranulocytosis, pancytopenia)

Immune system
Rare: Hypersensitivity (e.g. angioedema)

Psychiatric disorders
Common: 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 behavior, emotional disturbances, suicide attempt, suicide ideation

Nervous system disorders
Common: Somnolence, decreased alertness, ataxia, dizziness, headache, dysgeusia, amnesia
Frequency not known: Extrapyramidal 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 increased

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
Common: Fatigue

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9. Overdose

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

Signs and Symptoms
Depending on the dose ingested, intoxication with benzodiazepines is usually manifested by various degrees of central nervous system depression ranging from somnolence, mental confusion, dysarthria and lethargy, impaired vision and dystonia to ataxia, unconsciousness, central respiratory and/or circulatory depression and 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 (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is not an advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

General supportive and symptomatic measures are recommended.

Special attention should be paid to respiratory and cardiovascular functions in intensive care.

The value of dialysis has not been determined and is expected to be low for Dalmane. 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.
The physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and cyclic antidepressant overdose.
When taken with centrally-acting drugs, especially alcohol, the effects of over-dosage are likely to be more severe and, in the absence of supportive measures, may prove fatal.

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 with tension, excitement, anxiety attenuating properties and sedative and hypnotic effects. Flurazepam shows muscle relaxant and anticonvulsant effects.

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

Psychomotor studies have demonstrated that a dose of 15 mg given for 7 consecutive nights did not significantly affect performance on the morning after final administration. However, impairment of performance was recorded on the morning after final administration of 30 mg for 7 consecutive nights. This latter dose is associated with daytime anxiolytic effects.

5.2. Pharmacokinetic properties

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 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 plasma protein binding is high for flurazepam, N1-desalkyl-flurazepam and N1-hydroxyethyl-flurazepam.

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 were obtained (71-289 hours).

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 verses the 1st day.

Flurazepam monohydrochloride and its metabolites are eliminated primarily by renal excretion.

5.3. Preclinical safety data

Mutagenic and tumorigenic potential:
There is no sufficient set of investigations into the mutagenic potential of flurazepam available. Nevertheless, all available investigations are negative. There are no long-term carcinogenicity studies available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Talc
Magnesium stearate
Gelatin
Black iron oxide (E172)
Titanium dioxide (E171)

Printing ink:
Shellac
Red iron oxide (E172)
Ammonia Solution
Potassium Hydroxide
Propylene glycol

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 plastic securitainers - 1 year.

6.4. Special precautions for storage

Blisters: Do not store above 25°C. Store in the original package.
Bottles/containers: Do not store above 25°C. Keep the container tightly closed.

6.5. Nature and contents of container

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

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited,
Unit 35/36, Grange Parade,
Baldoyle Industrial Estate,
Dublin 13,
Ireland

8. MARKETING AUTHORISATION NUMBER

PA2010/039/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1977

Date of last renewal: 01 April 2007

10. DATE OF REVISION OF THE TEXT

August 2018