SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nabilone 0.25mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.25 mg of Nabilone.
For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Opaque green, size 2 hard gelatin capsule cap imprinted with “NAB 0.25” and opaque white body imprinted with “NAB 0.25”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nabilone is indicated for the control of nausea and vomiting, caused by chemotherapeutic agents used in the treatment of cancer, in patients who have failed to respond adequately to conventional antiemetic treatments.

4.2 Posology and method of administration

Nabilone is for administration to adults only. It is not recommended for use in children younger than 18 years of age as safety and efficacy have not been established.

The usual adult dosage is 1 mg or 2 mg twice a day. To minimise side-effects, it is recommended that the lower starting dose is used and that the dose is increased as necessary. The first dose should be administered the night before initiation of chemotherapy, and the second dose should be given one to three hours before the first dose of the oncolytic agent is administered.

The maximum daily dose should not exceed 6 mg, given in three divided doses.

Nabilone may be administered throughout each cycle of chemotherapy and, if necessary, for 48 hours after the last dose of each cycle. Data on the chronic use of nabilone are not available.

The elderly as for adults (see 'precautions').

4.3 Contraindications

Nabilone is contra-indicated in patients with a known allergy to cannabinoid agents and when the nausea and vomiting arises from any cause other than cancer chemotherapy.

4.4 Special warnings and precautions for use

As nabilone is excreted primarily by the biliary route, the drug is not recommended for use in patients with severe liver dysfunction.

Patients receiving nabilone should be closely observed, if possible, within an inpatient setting. This is especially important during the treatment of naive patients. However, even patients experienced with cannabinoid agents may have serious untoward responses not predicted by prior uneventful exposures. Patients should be made aware of possible changes of mood and other adverse behavioural effects of the drug.

Since nabilone can elevate supine and standing heart rates and cause postural hypotension, it should be used with caution in the elderly and in patients with hypertension and heart disease.

4.5 Interaction with other medicinal products and other forms of interaction

Nabilone should be administered with caution to patients who are taking other psychoactive drugs or CNS depressants, including alcohol, barbiturates and narcotic analgesics, or to those with a history of psychiatric disorder (including manic-depressive illness and schizophrenia). Nabilone has been shown to have an additive CNS depressant effect when given with either diazepam, secobarbitone sodium, alcohol or codeine.

4.6 Fertility, pregnancy and lactation

Usage in pregnancy: Laboratory studies have so far shown no evidence of teratogenicity. There are no adequate and well controlled studies in pregnant women. Nabilone should be used during pregnancy only if clearly needed.

Reproduction studies performed in rats at 150 times the human dose and rabbits at 40 times the human dose revealed a dose-related reduction in litter size, an increase in the incidence of foetal resorptions, and an increase in the incidence of stillborn pups. The number of implantations was unaffected by treatment. These effects appear related to the dose-dependent reduction in maternal food intake and gain in body weight induced by nabilone. At 150 times the maximum recommended human dose, nabilone produced a reduction in neonatal survival that may be related to reduced milk production by mothers. Nabilone is known to have an inhibitory effect on

prolactin release, which could contribute to the observed reduction in milk production. Hypothermia was also reported in the offspring of high-dose groups of female rats, which may have also contributed to reduced neonatal survival.

Nursing mothers: It is not known whether this drug is excreted in breast milk. It is not recommended that nabilone be given to nursing mothers.

4.7 Effects on ability to drive and use machines

Nabilone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as operating machinery or driving a car; therefore the patient should be advised accordingly. The effects of Nabilone may persist for a variable and unpredictable period of time following its oral administration. Adverse psychiatric reactions can persist for 48 to 72 hours following cessation of 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,
- 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

During controlled clinical trials of nabilone, virtually all patients experienced at least one adverse reaction. These included pyschotomimetic reactions.

In these trials, the commonest statistically significant adverse events (in decreasing order of incidence) were: drowsiness, vertigo/dizziness, euphoria (high), dry mouth, ataxia, visual disturbance, concentration difficulties, sleep disturbance, dysphoria, hypotension, headache and nausea.

Other reported events include confusion, disorientation, hallucinations, psychosis, depression, decreased co-ordination, tremors, tachycardia, decreased appetite and abdominal pain.

Tolerance to such CNS effects as relaxation, drowsiness and euphoria develops rapidly and is readily reversible.

Drug abuse and dependence: Nabilone is an abusable substance, capable of producing subjective side-effects, such as euphoria or "high", at therapeutic doses. Prescriptions should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a

few days). The physical dependence capability of Nabilone is unknown. Patients who participated in clinical trials, up to 5 days duration, showed no withdrawal symptoms on cessation of dosing.

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.

4.9 Overdose

Signs and symptoms are an extension of the psychotomimetic and physiological effects of nabilone. Overdosage may be considered to have occurred, even at prescribed dosages, if disturbing psychiatric symptoms are present. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing, possibly at a lower dose, may then be resumed if clinically indicated. In controlled clinical trials, alterations in mental status, related to the use of nabilone, resolved within 72 hours without specific medical therapy. Vital signs should be monitored, since hypertension, hypotension and tachycardia have occurred.

No cases of overdosage with more than 10 mg/day of nabilone have been reported during clinical trials. Signs and symptoms to be anticipated in large overdose situations are psychotic episodes, including hallucinations and anxiety reactions, respiratory depression and coma.

Treatment Conservative management, if possible (i.e. verbal support and comfort). In more severe cases, antipsychotic drugs may be useful, although they have not been systematically evaluated. Such patients should be closely monitored because of the potential for drug interactions (eg., additive CNS depressant effects due to nabilone and chlorpromazine).

General supportive care is recommended. Consider giving activated charcoal to decrease absorption from the gastrointestinal tract. The use of forced diuresis, pentoneal dialysis, haemodialysis, charcoal haemoperfusion, or cholestyramine, has not been reported. Most of a dose of nabilone is eliminated through the biliary system.

Treatment for respiratory depression and comatose state consists of symptomatic and supportive therapy. Attention should be paid to the occurrence of hypothermia. Consider fluids, inotropes and/or vasopressors for hypotension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nabilone is a synthetic cannabinoid which has been shown to have significant anti-emetic activity in patients undergoing chemotherapy for malignant neoplasms. The mode of action of nabilone has been studied in cats and dogs. Although its anti-emetic action is not yet fully understood, it is apparent that there are a number of

points in the control systems of the body at which nabilone could block the emetic mechanism.

5.2 Pharmacokinetic properties

Absorption

Two fasted subjects were given an oral dose of 2 mg ^{14}C-nabilone. Nabilone was readily absorbed from the gastrointestinal tract. Pharmacokinetic comparison between the oral and intravenous routes of administration suggested that most of the drug was available after oral dosage. Similarly, the percentages of radioactivity in the faeces and urine were approximately sixty per cent and twenty-four per cent respectively whichever route was employed, supporting the view that most of the oral dose was absorbed.

Half-life

The plasma half-life of unchanged nabilone in these volunteers was approximately two hours. The estimated half-life of the carbinol metabolite was somewhat longer at between five and ten hours. Total radioactivity had a half-life of approximately thirty-five hours.

Transport

The rapid disappearance of absorbed drug from the plasma has been related to extensive tissue distribution and to rapid metabolism and excretion.

Metabolism

Two metabolic pathways have been suggested. The major pathway probably involves the direct oxidation of nabilone to produce hydroxylic and carboxylic analogues. These compounds are thought to account for the remaining plasma radioactivity when carbinol metabolites have been extracted.

Excretion

When 2 mg of ^{14}C-nabilone was administered orally, over sixty per cent of the total radioactivity was eliminated in the faeces and about twenty five per cent in the urine. The discrepancy is probably due to additive analytical errors, since respiratory ^{14}C CO_2 did not account for the remaining fifteen per cent. Comparison with intravenous administration indicated no significant differences in the excretion pattern suggesting the biliary system to be the major excretory pathway.

5.3 Preclinical safety data

Monkeys treated with nabilone at doses as high as 2 mg/kg/day for a year experienced no significant adverse events. This result contrasts with the finding in a planned 1-year dog study that was prematurely terminated because of deaths associated with

convulsions in dogs receiving as little as 0.5 mg/kg/day. The earliest deaths, however, occurred at 56 days in dogs receiving 2 mg/kg/day. The unusual vulnerability of the dog is not understood; it is hypothesised, however, that the explanation lies in the fact that the dog differs markedly from other species (including humans) in its metabolism of nabilone.

Carcinogenesis, Muta genesis, Impairment of Fertility Carcinogenicity studies have not been performed with nabilone. The influence on fertility and reproduction at doses of 150 and 40 times the maximum recommended human dose was evaluated in rats and rabbits, respectively. In these studies there was no evidence of teratogenicity due to nabilone. In high dose groups, however, nabilone produced a slight decrease in mean litter size, although the number of implantations was unaffected by treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone

Pre-gelatinised Starch

Isopropyl alcohol

Capsule Shell Components
Gelatin

Water

Indigo carmine (E132)

Quinoline yellow (E104)

Titanium Dioxide (E171)

Printing Ink Composition
Shellac

Propylene glycol

Black iron oxide (E172)

Potassium hydroxide

6.2 Incompatibilities

None known.

6.3 Shelf life

3 Years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

HDPE container with CRC closure or Alu//Alu/PVC/OPA blister pack of 20 capsules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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