SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dexamfetamine Sulfate 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains 5mg Dexamfetamine Sulfate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Plain white uncoated flat bevelled edged tablet, one side plain and one side score and embossed with "D5".

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dexamfetamine Sulfate is a sympathomimetic amine with central stimulant and anorectic activity. It is indicated in narcolepsy. It is also indicated for children with refractory hyperkinetic states under the supervision of a physician specialising in child psychiatry.

4.2 Posology and method of administration

For oral administration.

Adults: In narcolepsy, the usual starting dose is 10mg dexamfetamine sulfate a day, given in divided doses. Dosage may be increased if necessary by 10mg a day at weekly intervals to a suggested maximum of 60mg a day.

Elderly: Start with 5mg a day, and increase by increments of 5mg at weekly intervals.

Children: In hyperkinetic states, the usual starting dosage for children aged 3-5 years is 2.5mg a day, increased if necessary by 2.5mg a day at weekly intervals; for children aged 6 years and over, the usual starting dose is 5-10mg a day increasing if necessary by 5mg at weekly intervals.

The usual upper limit is 20mg a day though some older children have needed 40mg or more for optimal response.

4.3 Contraindications

- Hypersensitivity to dexamfetamine or other amfetamine derivatives or any of the excipients.
- Patients with symptomatic cardiovascular disease, structural cardiac abnormalities and/or moderate or severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- Cerebrovascular disorders (cerebral aneurysm, vascular abnormalities including vasculitis or stroke)
- Patients with advanced arteriosclerosis.
- During or for 14 days after treatment with an MAO inhibitor.
- Patients with a history of drug abuse or alcohol abuse.
- Patients with hyperthyroidism, glaucoma, porphyria or hyperexcitability.
- Patients with Gilles de la Tourette syndrome or similar dystonias.
- Severe depression, anorexia nervosa/anorexic disorders, suicidal ideation, hyperexcitability, psychotic symptoms, severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled), schizophrenia, psychopathic/borderline personality disorder.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Precautions to be taken before handling or administering the medicinal product

Pre-treatment screening:

Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4)

Ongoing monitoring

Growth, psychiatric and cardiovascular status should be continuously monitored (see also Section 4.4).

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;
- Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;
- Development of de novo or worsening of pre-existing psychiatric disorders, including depression and aggressive behaviour, should be monitored at every adjustment of dose and then at least every 6 months and at every visit. Patients should be monitored for the risk of diversion, misuse, and abuse of dexamfetamine

Long-term use (more than 12 months) in children and adolescents

Cardiomyopathy has been reported with chronic amfetamine use.

The safety and efficacy of long-term use of dexamfetamine has not been systematically evaluated in controlled trials. Dexamfetamine treatment should not be and does not need to be indefinite. Dexamfetamine treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4 for cardiovascular status, growth, appetite, and development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal, and excessive perseveration.

The physician who elects to use dexamfetamine for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the medicinal product for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that dexamfetamine is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

Cardiovascular status

Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exceptional chest pain, unexplained syncope, dyspnoea, or other symptoms suggestive of cardiac disease during dexamfetamine treatment should undergo a prompt specialist cardiac evaluation.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

Treatment with stimulants in general may lead to a minor increase in blood pressure (approx. 2-4 mm Hg) as well as an increase in heart rate (approx. 3-6 beats/minute).

In few patients, these values may be higher.

The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See section 4.3 for conditions in which dexamfetamine treatment in contraindicated.

The use of dexamfetamine is contraindicated in certain pre-existing cardiovascular disorders unless specialist paediatric cardiac advice has been obtained (see section 4.3).

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders.

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the onset of sympathomimetic effects of a stimulant medicine (see section 4.3).

Use with caution in patients on guanethidine and patients with mild hypertension or a family history of dystonias. If tics develop, discontinue treatment with dexamfetamine Sulfate. Dexamfetamine is likely to reduce the convulsant threshold therefore caution is advised in patients with epilepsy. Height and weight should be carefully monitored in children as growth retardation may occur. Children who are not gaining weight as expected should have their treatment interrupted temporarily.

Caution should be used when administering dexamfetamine to patients with impaired kidney function or unstable personality.

Drug dependence, with consumption of increasing doses to levels many times those recommended, may occur as tolerance develops. At such levels, a psychosis which may be clinically indistinguishable from schizophrenia can occur.

Treatment should be stopped gradually since abrupt cessation may produce extreme fatigue and mental depression.

Cardiomyopathy has been reported with chronic amfetamine use.

Due to the potential decreased appetite associated with dexamfetamine use, caution is advised in the presence of anorexia nervosa.

Pre-existing structural cardiac abnormalities:

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products are not recommended in children, adolescents, or adults with known structural cardiac abnormalities (*see 4.3, Contraindications*).

Blood pressure should be monitored at appropriate intervals in all patients taking dexamfetamine, especially those with hypertension.

Psychiatric adverse events:

- Administration of stimulants may exacerbate symptoms of behaviour disturbance and thought disorders in patients with a pre-existing psychotic disorder.

- Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.
- Treatment emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking or mania in children or adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant and discontinuation of treatment may be appropriate.
- Patients beginning treatment with stimulants for ADHD should be monitored for the appearance, or worsening of, aggressive behaviour or hostility.

4.5 Interaction with other medicinal products and other forms of interaction

Adrenoreceptor blocking agents (e.g. propanolol), lithium and α methyltyrosine may antagonise the effects of dexamfetamine. Disulfiram may inhibit metabolism and excretion.

The concurrent use of tricyclic antidepressants may increase the risk of cardiovascular side effects.

Concurrent use of MAOI's or use within the preceding 14 days may precipitate a hypertensive crisis.

Concurrent use of beta-blockers may result in severe hypertension and dexamfetamine may result in diminished effect of other anti-hypertensives such as guanethidine.

Phenothiazines may inhibit the actions of dexamfetamine.

Amfetamines may delay the absorption of ethosuximide, phenobarbital and phenytoin.

Acute dystonia has been noted with concurrent administration of haloperidol.

Haloperidol blocks dopamine and norepinephrine re-uptake, thus inhibiting the central stimulant effects of amfetamines.

The analgesic effect of morphine may be increased and its respiratory depressant effects decreased with concurrent use of morphine and dexamfetamine.

Amfetamines potentiate the analgesic effects of meperidine.

Concomitant administration of clonidine and dexamfetamine may result in an increased duration of action of dexamfetamine.

Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of dexamfetamine. Urinary acidifying agents (ammonium chloride, sodium acid phosphate, etc.) increase urinary excretion of dexamfetamine. Both groups of agents lower blood levels and efficacy of dexamfetamine.

Gastrointestinal alkalizing agents (sodium bicarbonate, etc) increase the absorption of amfetamines. Urinary alkalizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amfetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and efficacy of amfetamines.

Alcohol may exacerbate the CNS adverse reactions of psychoactive drugs, including dexamfetamine. It is therefore advisable for patients to abstain from alcohol during treatment.

Chlorpromazine blocks dopamine and norepinephrine re-uptake, thus inhibiting the central stimulant effects of amfetamines, and can be used to treat amfetamine poisoning.

Drug/laboratory test interactions

Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

4.6 Fertility, Pregnancy and lactation

Dexamfetamine has been thought to produce embroytoxic effects in rodents and retrospective evidence of certain significance in man has suggested a similar possibility.

Dexamfetamine Sulfate is contraindicated during pregnancy.

There is a limited amount of data from the use of dexamfetamine in pregnant women.

Data from a cohort study of in total approximately 5570 pregnancies exposed to amphetamine in the first trimester do not suggest an increased risk of congenital malformation. Data from another cohort study in approximately 3100 pregnancies exposed to amphetamine during the first 20 weeks of pregnancy, suggest an increased risk of preeclampsia, and preterm birth.

Newborns exposed to amphetamine during pregnancy may experience withdrawal symptoms.

Children of mothers who are dependent on amfetamine have been shown to be at an increased risk of premature birth and reduced birth weight.

Moreover, these children may develop withdrawal symptoms like dysphoria, including hyperexcitability and pronounced exhaustion.

Dexamfetamine Sulfate passes into breast milk.

Because of the potential for adverse reactions in nursing infants from dexamfetamine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Dexamfetamine Sulfate may affect ability to drive or operate machinery.

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

Cardiac disorders: cardiomyopathy, myocardial infarction, palpitations, tachycardia

Eye disorders: mydriasis, visual disturbance

Gastrointestinal disorders: abdominal cramps, colitis ischaemic, diarrhoea, dry mouth, nausea

General disorders and administration site conditions: chest pain, death due to cardiovascular collapse, growth retardation, hyperpyrexia, hypersensitivity including angioedema and anaphylaxis, sudden death *(see 4.4, Special Warnings and Special Precautions for Use).*

Investigations: blood pressure decreased, blood pressure increased

Metabolism and nutrition disorders: acidosis, anorexia, weight loss.

Musculoskeletal and connective tissue disorders: rhabdomyolysis

Nervous system disorders: ataxia, choreoathetoid movements, concentration difficulties, convulsion, dizziness, dyskinesia, dysgeusia, fatigue, headache, hyperactivity,

hyperreflexia,intracranial haemorrhage, neuroleptic malignant syndrome, stroke, tremor, Tourette's syndrome

Psychiatric disorders: aggressive behaviour, anxiety, confusion, delirium, depression, drug dependence, dysphoria, emotional lability, euphoria, hallucination, impaired cognitive test performance, insomnia, irritability, libido altered, nervousness, night terrors, obsessive-compulsive behaviour, panic states, paranoia, psychosis/ psychotic reactions, restlessness, tics

Renal and urinary disorders: renal damage

Reproductive system and breast disorders: impotence

Skin and subcutaneous tissue disorders: alopecia, rash, sweating, urticaria

Vascular disorders: cardiovascular collapse, cerebral vasculitis, Raynaud's phenomenon (not known)

A toxic hypermetabolic state, characterised by transient hyperactivity, hyperpyrexia, acidosis and death due to cardiovascular collapse have been reported.

Cessation of, or reduction in, amfetamine use that has been heavy and prolonged can result in withdrawal symptoms. Symptoms include dysphoric mood, fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, psychomotor retardation or agitation, anhedonia and drug craving.

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

4.9 Overdose

In acute overdosage, the adverse effects are accentuated and may be accompanied by hyperpyrexia, mydriasis, hyperreflexia, chest pain, tachycardia, cardiac arrhythmias, confusion, panic states, aggressive behaviour, hallucinations, delirium, convulsions, respiratory depression, coma, circulatory collapse, and death.

Individual patient response may vary widely and toxic manifestations may occur with quite small overdoses.

Treatment consists of the induction of vomiting and/or gastric lavage together with supportive and symptomatic measures. Excessive stimulation or convulsions may be treated with diazepam. Excretion of dexamfetamine may be increased by forced acid diuresis. Chlorpromazine antagonises the central stimulant effects of amfetamines and can be used to treat amfetamine intoxication.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N06BA02

Pharmacotherapeutic group: Centrally acting sympathomimetics;

Dexamfetamine Sulfate is a sympathomimetic amine with a central stimulant and anorectic activity.

5.2 Pharmacokinetic properties

Dexamfetamine is readily absorbed from the gastrointestinal tract. It is resistant to metabolism by monoamine oxidase. It is excreted in the urine as unchanged parent drug together with some hydroxylated metabolites. Elimination is increased in acidic urine. After high doses, elimination in the urine may take several days.

5.3 Preclinical safety data

Dexamfetamine has been thought to produce embryotoxic effects in rodents, and retrospective evidence of uncertain significance in man has suggested a similar possibility. Dexamfetamine Sulfate passes into breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (PH102)

Calcium Hydrogen Phosphate Dihydrate

Povidone

Maize Starch

Magnesium Stearate

6.2 Incompatibilities

None stated

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Polypropylene container with a polypropylene lid containing 28 or100 tablets or Alu/PVC blisters of 28 Tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Brown & Burk UK Ltd

5 Marryat Close

Hounslow West

Middlesex

TW4 5DQ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0152

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24/08/2016

10 DATE OF REVISION OF THE TEXT

26/07/2022