SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenylbutazone 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sugar coated tablet contains 200mg Phenylbutazone .

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

White, sugar coated, biconvex tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ankylosing spondylitis

Phenylbutazone should only be used where other therapies have been found unsuitable.

Route of administration: oral.

4.2 Posology and method of administration

For oral administration. To be taken preferably with or after food.

Dosage:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
When long term treatment is unavoidable special precautions should be taken (see section 4.4) and the dosage should be adjusted to the needs of each patient taking account of the patient's age and general condition.

Phenylbutazone tablets should be swallowed whole with a meal together with liquid. Patients with sensitive stomachs should be given sodium-free antacid at the same time.

Adults: for the initial 48 hours 400-600mg daily in divided doses. Thereafter, reduce to the minimum amount necessary, usually 200-300mg daily in divided doses.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy

Children: not recommended for children under 14 years.

4.3 Contraindications

- Hypersensitivity to phenylbutazone or to any of the excipients.

- Patients who have shown hypersensitivity reactions or in asthmatic patients in whom attacks of asthma, urticaria, angioedema or acute rhinitis are precipitated by non-steroidal anti-inflammatory drugs including acetylsalicylic acid and ibuprofen or by other drugs with prostaglandin synthetase inhibiting activity.

- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

- Use with other NSAIDs including cyclooxygenase-2 selective inhibitors (see section 4.5).

- Patients with symptoms or a history of inflammatory bowel disease with or without ulceration as these conditions may be exacerbated (see section 4.8).

- Blood dyscrasias and/or haemorrhagic diathesis.

- Severe heart failure, hepatic or renal failure (see section 4.4); or pulmonary insufficiency, oedema or hypertension, where there is danger of cardiac decompensation.

- Last trimester of pregnancy (premature closure of ductus arteriosus – see section 4.6).

- Thyroid disease.

- Sjogrens' syndrome.

4.4 Special warnings and precautions for use

Phenylbutazone should be used only under close medical supervision.

Minimising undesirable effects

In all patients: Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below).

Elderly patients are generally more prone to adverse reactions, especially gastro-intestinal bleeding and perforation which may be fatal (see section 4.2). Particular caution should be exercised.

Blood dyscrasias

Blood dyscrasias may occur suddenly after a small dose or insidiously after prolonged therapy particularly in the elderly. If treatment is expected to continue for more than one week, blood counts should be monitored before and regularly during therapy. If significant changes occur e.g. decrease in leucocyte and/or platelet counts or in the haematocrit, phenylbutazone should be withdrawn. Therapy should also be stopped if symptoms suggestive of a dycrasia arise (e.g. bruising, fever, sore throat, rash, mouth ulceration), and patients should be advised of this.

Granulocytopenia or aplastic anaemia have to be excluded in patients with stomatitis before treatment with phenylbutazone is started, as stomatitis might

indicate a pre-existing haematological abnormality of this type.

Gastro-intestinal bleeding, ulceration and perforation

Serious gastro-intestinal reactions such as bleeding, ulceration and perforation, which can be fatal, have been reported with NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Although minor upper gastrointestinal reactions such as dyspepsia are common, usually developing early in therapy, physicians should watch for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous gastro-intestinal tract symptoms. If any of the symptoms or signs suggestive of gastro-intestinal toxicity occur, phenylbutazone should be discontinued immediately.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin (see section 4.5). Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients.

When GI bleeding or ulceration occurs in patients receiving phenylbutazone, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

The use of phenylbutazone with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided (see section 4.5).

Respiratory disorders

NSAIDs inhibit prostaglandin synthetase activity and can precipitate acute attacks of bronchospasm in patients suffering from, or with a previous history of, bronchial asthma. Caution is required when administering phenylbutazone to these patients.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for phenylbutazone.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with phenylbutazone after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Cardiovascular, renal & hepatic impairment

NSAIDs cause dose dependent reduction in prostaglandin formation, can cause oedema and fluid/sodium retention and may precipitate renal failure. Patients at greatest risk are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see section 4.3 and Monitoring – blood tests, below).

Severe hepatic reactions including jaundice and hepatitis have been reported with phenylbutazone. If abnormal liver tests (see below Monitoring – blood tests) persist or worsen, or clinical signs and symptoms consistent with liver disease develop, the drug should be discontinued.

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with NSAIDSs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in most cases within the first month of treatment. Phenylbutazone should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Monitoring - blood tests

If phenylbutazone is given for more than one week, liver function tests, kidney function tests and blood counts should be performed periodically. If significant changes occur, the drug should be withdrawn.

Connective tissue disorders/SLE

Patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders may be at an increased risk of aseptic meningitis (see section 4.8)

Impaired female fertility

The use of phenylbutazone may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of phenylbutazone should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Other analgesics including cyclooxygenase-2-selective inhibitors: concomitant use of phenylbutazone and other NSAIDs (including cyclooxygenase-2 selective inhibitors and aspirin) is contra-indicated because of an increased risk of adverse effects (see section 4.4).

Corticosteroids: Increased risk of GI ulceration and GI bleeding (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Antiplatelet agents: increased risk of gastro-intestinal bleeding (see section 4.4).

Selective serotonin reuptake inhibitors (SSRIs): increased risk of gastro-intestinal bleeding (see section 4.4).

Anti-hypertensives: Reduced anti-hypertensive effect due to inhibition of vasodilatory prostaglandin synthesis.

Diuretics: Reduced diuretic effect. Diuretics can also increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Cholestyramine: Reduced enteral absorption of phenylbutazone.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity (possibly mediated through combined renal antiprostaglandin effects of both drugs).

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as they can reduce the effect of mifepristone.

Misoprostol: When given concomitantly, phenylbutazone and misoprostol may induce adverse symptoms related to the central nervous system, such as dizziness, headache and transient diplopia.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Methylphenidate: When phenylbutazone is given with methylphenidate the serum concentration of metabolite oxyphenbutazone rises and the elimination half life of phenylbutazone is prolonged.

Alcohol: Phenylbutazone may potentiate the effects of alcohol on the central nervous system

Anabolic steroids: During concomitant administration of anabolic steroids and phenylbutazone, the serum concentration of the metabolite oxyphenbutazone rises.

Phenytoin: By competitive displacement from their serum-protein binding sites, phenylbutazone may increase the effects and duration of effects of phenytoin. It may also inhibit the metabolic degradation of phenytoin.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Drugs for diabetes mellitus: By competitive displacement from their serum-protein binding sites, phenylbutazone may increase the effects and duration of effects of oral antidiabetic drugs. Also it may potentiate the effects of insulin.

Drugs that activate hepatic microsomal enzymes: In patients previously treated with drugs which activate the hepatic microsomal enzyme e.g. barbiturates, chlorpheniramine, rifampicin, promethazine and corticosteroids (e.g. prednisolone) the elimination half-life of phenylbutazone is shortened

Interference with investigations: Phenylbutazone displaces thyroid hormone from its serum protein-binding sites and may make it more difficult to interpret thyroid function tests.

4.6 Fertility, pregnancy and lactation

Pregnancy
Phenylbutazone may appear in cord blood and congenital abnormalities have been reported in association with NSAIDs in man; however, these are low in frequency and do not appear to follow any discernible pattern.

During the first and second trimester of pregnancy, phenylbutazone should not be given unless clearly necessary. From the 20th week of pregnancy onward, phenylbutazone use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. If phenylbutazone is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to phenylbutazone for several days from gestational week 20 onward. Phenylbutazone should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

Phenylbutazone is contraindicated in the last trimester of pregnancy (see below and section 4.3 'Contraindications') as NSAIDs:

- Expose the foetus to cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- may delay the onset of labour and increase its duration
- may increase the bleeding tendency in both mother and child (see section 4.3 'Contraindications')
- Renal dysfunction (see above).

During the third trimester of pregnancy, phenylbutazone may expose the mother and the neonate, at the end of pregnancy, to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Phenylbutazone is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breast-feeding.

Fertility
See section 4.4 'Special warnings and precautions for use', regarding female fertility.

4.7. Effects on ability to drive and use machines

Patients receiving treatment with phenylbutazone should be warned that drowsiness, dizziness, fatigue and visual disturbances may occur, in which case they should not drive, operate potentially dangerous machinery, or engage in other activities that may become hazardous because of decreased alertness. Concomitant ingestion of alcohol may potentiate these effects.

4.8 Undesirable effects

Gastrointestinal:
Gastrointestinal disorders are the most commonly observed adverse events. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4 'Special warnings and precautions for use'). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 'Special warnings and precautions for use') have been reported. Less frequently, gastritis has been observed. Isolated cases of pancreatitis, oesophagitis, oesophageal ulcer, benign stricture of the oesophagus and small bowel obstruction have also been reported.

Hypersensitivity:
Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) associated skin disorders including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including Stevens Johnson syndrome, epidermal necrolysis and erythema multiforme). Isolated cases of serum sickness, lymphadenopathy, vasculitis, systemic lupus erythematosus-like syndrome, eosinophilic pulmonary infiltrates and fever have also been reported.

Cardiovascular and cerebrovascular:
Oedema, hypertension and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4 'Special warnings and precautions for use').
Rare: congestive heart failure, pulmonary oedema.
Isolated cases: hypertension, myocarditis, pericarditis.

Body as a whole:
Frequent: oedema, water / sodium retention.

Endocrine system:
Occasional: goitre, lowering of plasma thyroid hormone concentration.
Isolated cases: hypothyroidism.

Neurological and special senses:
Visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic

meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever, or disorientation (see section 4.4 'Special warnings and precautions for use'), depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise and drowsiness.
Isolated cases: peripheral neuropathy, excitation, blurred vision, retinal haemorrhage, hearing loss.

Haematological:
Rare: anaemia due to occult gastrointestinal blood loss, haemolytic anaemia, thrombocytopenia, neutropenia, agranulocytosis, leucopenia, pancytopenia, bone marrow depression, aplastic anaemia.

Hepatic:
Rare: increase in serum transaminases, hepatitis and jaundice.
Isolated cases: fulminant hepatitis.
Frequency unknown: abnormal liver function.

Renal
Rare: impaired renal function, acute renal failure, haematuria, proteinuria.
Isolated cases: acute tubular necrosis, acute interstitial nephritis, nephrotic syndrome, glomerulonephritis, papillary necrosis, ureteral obstruction with uric acid crystal formation.
Frequency unknown: nephrotoxicity in various forms.

Respiratory tract:
Isolated cases: exacerbation of bronchial asthma and of an "acute pulmonary syndrome" – marked by dyspnoea, fever, shadows in radiographs of the lungs and sometimes also by eosinophilia have been reported. Although a casual relationship with the latter has not been proven, the drug should be withdrawn at first signs of this potentially serious syndrome for the treatment of which corticosteroids and supportive cardiotherapy may be necessary.

Dermatological :
Very rare: bullous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis.
Frequency unknown: photosensitivity.

Others:
Occasional stomatitis.
Rare: salivary gland enlargement, dry mouth.

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

Symptoms
Gastro-intestinal: Nausea, vomiting, epigastric pain, rarely diarrhoea, gastrointestinal bleeding, peptic ulceration.

CNS: Tinnitus and deafness, headache, dizziness, drowsiness, disorientation, excitation, fainting, hyperventilation and sweating, agitation, coma, occasionally convulsions.

Haematologic: Anaemia, leucopenia, thrombocytopenia, hypoprothrombinaemia.

Cardiac: Hypotension (occasionally hypertension), tachycardia, cardiac arrhythmias.

Pulmonary: Adult respiratory distress syndrome, cyanosis.

Acid-base/Electrolyte: Metabolic acidosis and respiratory alkalosis. hyperglycaemia, hypocalcaemia,

Hepatic: Hepatotoxicity including elevated transaminases, jaundice and hepatic necrosis which may be delayed.

Renal: Renal toxicity, acute renal failure, urinary retention. Urine may be discoloured red due to a metabolite.

Effects in severe poisoning may last for days, or even weeks.

Therapeutic measure
For adults ingesting >1 g, gastric lavage followed by 50 g activated charcoal is recommended within one hour of ingestion.
For adults ingesting < 1 g, activated charcoal should be considered within one hour of ingestion.
For children ingesting >100 mg, 10-15 g of activated charcoal is recommended.

Observation for 36 hours may be required due to the delayed effects. Care should be symptomatic and supportive. Frequent or prolonged convulsions should be treated with intravenous diazepam. Check and correct urine and electrolytes, pH, blood gases. Maintain good urine output. Monitor hepatic and renal function. Treat hypotension with fluids, taking care not to over-hydrate (oedema secondary to renal failure may occur). Cardiac monitoring is required in symptomatic patients. In severe cases charcoal haemoperfusion may be considered

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Phenylbutazone has analgesic, antipyretic and anti-inflammatory properties; however, because of its toxicity it is not employed as a general analgesic or antipyretic. Although phenylbutazone is effective in almost all rheumatic disorders including ankylosing spondylitis, acute gouty arthritis, osteoarthritis, rheumatoid arthritis, and Reiters' disease it should only be used in acute rheumatic disorders, where less toxic drugs have failed. In the United Kingdom the use of phenylbutazone is restricted to the treatment in hospital of ankylosing spondylitis.

5.2. Pharmacokinetic properties

Phenylbutazone is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 2 hours after ingestion. At therapeutic plasma concentrations phenylbutazone is 98% bound to plasma proteins; at higher concentrations the fraction bound decreases. It is extensively metabolised in the liver by oxidation and by conjugation with glucuronic acid.Oxyphenbutazone and y-hydroxyphenbutazone are formed by oxidation but only small amounts appear in urine, the remainder being further metabolised. About 1% of a dose is excreted in the urine as unchanged phenylbutazone, and about 10% is excreted in bile mainly as metabolites. The mean elimination half-life is about 70 hours but it is subject to large variations. Phenylbutazone crosses the placenta and appears in breast milk.

5.3. Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch, sodium laurilsulphate, gelatin, sucrose, colloidal anhydrous silica, purified talc, magnesium stearate, sodium starch glycollate, and a coating consisting of sucrose, purified talc, titanium dioxide, maize starch.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

60 months

6.4. Special precautions for storage

Store in a dry place not above 25ºC

6.5. Nature and contents of container

Securitainer containing 28 or 1000 tablets

6.6. Instruction for use and handling

None applicable

7. MARKETING AUTHORISATION HOLDER

Chemidex Pharma Limited
T/A Essential Generics or Chemidex Generics
Egham Business Village
Crabtree Road
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Surrey
TW20 8RB
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8. MARKETING AUTHORISATION NUMBER

PL 17736/0081

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/12/2008

10 DATE OF REVISION OF THE TEXT

26/06/2023