Applicant: Reckitt Benckiser Pharmaceuticals (Pty) Ltd
Product: Disprin Melts
Dosage: Tablets
Strength: 300 mg aspirin
PI Safety Update approval: 06 Feb 2024

CLEAN PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S0

1. NAME OF THE MEDICINE

DISPRIN® MELTS 300 mg Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg Aspirin per tablet.

Sugar free

Contains sweetener:

Saccharin 1.0 mg per tablet

For full list of excipients, see section 6.1

3. PHARMAEUTICAL FORM

Dispersible Tablets

White, circular, flat, bevelled edges tablet with matt finish and a sword imprinted on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DISPRIN MELTS are indicated for the relief of mild to moderate pain and/or fever.

4.2 Posology and method of administration

Posology

Use the lowest effective dose for the shortest possible duration of treatment

Adults: 1 to 3 tablets. Repeat 4 hourly if necessary but not more than 12 tablets to be taken during any 24 hour period.

Children 16 years and over: 1 to 3 not more than four times a day to a maximum of 10 tablets in 24 hours.

Warning: If symptoms persist for more than 10 days a medical practitioner should be consulted.

Method of administration

For oral administration.

DISPRIN MELTS disperses on the tongue without water.

4.3 Contraindications

DISPRIN MELTS is contraindicated in patients with:

- Hypersensitivity to aspirin or to any of the excipients listed (see section 6.1).
- Hypersensitivity to other non-steroidal anti-inflammatory medicines.
- Nasal polyps associated with asthma (high risk of severe sensitivity reactions).
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs including DISPRIN MELTS.
- Patients with active or history of recurrent gastrointestinal ulcer/haemorrhage/perforations.
- Patients with active or a history of peptic ulceration.
- Haemophilia.
- Severe hepatic impairment.
- Severe renal impairment.
- Heart failure.
- Children aged under 16 years due to a possible risk of Reye's syndrome, unless specifically indicated.
- Patients receiving oral anti-coagulant therapy.
- Pregnancy and lactation (see section 4.6).
- Combination with methotrexate at doses of 15 mg/week or more

4.4 Special warnings and precautions for use

DO NOT USE CONTINUOUSLY FOR MORE THAN 10 DAYS WITHOUT CONSULTING A DOCTOR.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Gastrointestinal effects: DISPRIN MELTS should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as their condition may be exacerbated. (see section 4.3)

Gastrointestinal bleeding, ulceration or perforation which can be fatal, has been reported with all NSAIDs including DISPRIN MELTS at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI, ulceration, perforation or bleeding (PUBs) is higher with increasing doses of DISPRIN MELTS, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. These patients should commence treatment on the lowest dose available.

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.

DISPRIN MELTS decreases platelet adhesiveness and increases bleeding time. Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin (see section 4.3), selective serotonin-reuptake inhibitors or anti-platelet medicines such as clopidogrel and ticlopidine.

When gastrointestinal bleeding or ulceration occurs in patients receiving DISPRIN MELTS, treatment with DISPRIN MELTS should be stopped immediately.

SLE and mixed connective tissue disease: Systemic lupus erythematosus and mixed connective tissue disease, due to increased risk of aseptic meningitis.

Dermatological effects: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, may occur. DISPRIN MELTS should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular effects: Caution is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertention and oedema have been reported in association with DISPRIN MELTS therapy.

In view of the DISPRIN MELTS inherent potential to cause fluid retention, heart failure may be precipitated or be worsened.

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Respiratory effects: Bronchospasm, skin eruptions, paroxysmal bronchospasm and dyspnoea may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Renal: Caution is advised in patients with renal impairment.

Hepatic: Caution is advised in patients with hepatic impairment.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including DISPRIN MELTS especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Impaired female fertility: May cause impairment of female fertility.

Patients with gout: The product should not be given to patients with gout, as serum urate may be increased and acute gout attacks may be precipitated, unless recommended by a healthcare professional.(see Interactions)

Pregnancy: Regular use of NSAIDs such as DISPRIN MELTS during the first and third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased.

Paediatric Use: There is an association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason, aspirin should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

Aspirin has been implicated in Reye's Syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A doctor should be consulted before aspirin is used in such patients.

Surgical procedures: DISPRIN MELTS should be stopped several days before scheduled surgical procedures due to increased bleeding time.

Interference with laboratory tests:

DISPRIN MELTS may produce falsely increased results for blood creatinine, urate and urea. Falsely decreased results may be obtained for blood thyroxine and urate (> 4 g/day aspirin) and for urinary 5-HIAA (with nitrosonaphthol method). Urinary VMA (HMMA) levels may be falsely increased or decreased depending on the method of analysis. Urinary glucose oxidase: Aspirin may cause a false negative test in the presence of glycosuria.

Aspirin and other salicylates can interfere with thyroid function tests.

DISPRIN MELTS should be administered with caution to patients with dyspepsia, anaemia and when the patient is dehydrated.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) :

Drug Reaction witj Eossinophillia and Systemic Symptoms (DRESS) has been reportd in patients taking NSADIs such as Disprin Melts. Somer of these events have been fatal or life-threatening. DRESS typically, althought not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Ther clinical manifestations may include hepatitis, nephritis, haematologocal abnormalities, myocarditis, or myosiditis. Somestimes symptoms of DRESS mayresemble an acute viral infection. Eosinophillia is often present. Because this disorder i variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue DISPRIN MELTS and evaluate the patient immediately.

4.5 Interaction with other medicines and other forms of interaction

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Calcium channel blockers: Reduced hypotensive effects, increased anti-platelet effects which may result in prolonged bleeding time.

Digoxin: NSAIDs including DISPRIN MELTS may exacerbate cardiac failure, reduce GFR and increase plasma digoxin levels.

Varicella vaccine: Avoid use of DISPRIN MELTS in varicella vaccine recipients due to a possible association with Reye's syndrome.

Antihypertensives (ACE inhibitors and Angiotensin II Antagonists and renin antagonists such as aliskiren) and diuretics: NSAIDs may reduce the effect of diuretics and decrease the blood pressure lowering effect of antihypertensive medicines.

In patients with compromised renal function and in dehydrated patients or elderly patients the co-administration of an ACE inhibitor or Angiotensin II antagonist and DISPRIN MELTS may result in further deterioration of renal function, including acute renal failure. These interactions should be considered in patients taking DISPRIN MELTS concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of DISPRIN MELTS.

Anti-coagulants: DISPRIN MELTS may enhance the effects of anti-coagulants, such as warfarin.

Anti-platelet medicines : increased risk of bleeding including gastrointestinal bleeding.

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Ibuprofen: Experimental data suggest that ibuprofen may inhibit the effect of DISPRIN MELTS on platelet aggregation when they are dosed concomitantly.

Other NSAIDs or other salicylates including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of DISPRIN MELTS and NSAIDs as this may increase the risk of adverse effects.

Ciclosporin: Increased risk of nephrotoxicity with DISPRIN MELTS.

Tacrolimus: Possible increased risk of nephrotoxicity when DISPRIN MELTS is given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when DISPRIN MELTS is given with zidovudine.

Metoclopramide & domperidone: May increase the rate of absorption of DISPRIN MELTS.

Valproate: DISPRIN MELTS may increase valproate levels resulting in valproate toxicity.

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

Uricosurics: DISPRIN MELTS inhibits the effects of uricosurics.

Mifepristone: DISPRIN MELTS can reduce the effect of mifepristone.

Methotrexate: Decreased elimination of methotrexate and increased methotrexate side effects.

Barbiturates and other sedatives: May mask the respiratory symptoms of DISPRIN MELTS and have been reported to enhance its toxicity. Prolonged use of high doses may lead to anaemia, blood dyscrasias, gastrointestinal heamorrhage, peptic ulceration and renal papiliary necrosis.

Antidiabetic Medicines, e.g. insulin, sulphonylureas:

Increased hypoglycaemic effect by high doses of DISPRIN MELTS via hypoglycaemic action of DISPRIN MELTS and displacement of sulphonylurea from its plasma protein binding sites.

Alcohol

Increased damage to gastro-intestinal mucosa and prolonged bleeding time due to additive effects of DISPRIN MELTS and alcohol.

Laboratory investigations: DISPRIN MELTS may interfere with some laboratory tests used to measure urine glycose.

4.6 Fertility, pregnancy and lactation

DISPRIN MELTS is contraindicated in pregnancy and lactation.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies show an increased risk of miscarriage and of cardiac

malformation and gastroschisis after use of a prostaglandin synthesis inhibitor such as DISPRIN MELTS in early pregnancy. DISPRIN MELTS is teratogenic in animals.

During the third trimester of pregnancy, DISPRIN MELTS may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis;

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.

Lactation

Use of DISPRIN MELTS is contraindicated in women breastfeeding their infants. DISPRIN MELTS given in breastfeeding mothers may pose a risk of Reye's syndrome in nursing infants

Fertility

Medicines such as DISPRIN MELTS which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effcets on ability to drive and use machines

DISPRIN MELTS has no or negligible influence-on ability to drive and use machines.

4.8 Undesirable-effects

System Organ Class	**Frequency**	**Adverse Events**
Blood and Lymphatic System Disorders	Not Known	Hypoprothrombinaemia, thrombocytopenia, aplastic anaemia, agranulocytosis, pancytopenia
Immune System Disorders	Not Known	Pyrexia, urticaria, pruritus, angioedema
Metabolism and Nutrition Disorders	Not Known	Sodium retention, fluid retention

Nervous System Disorders	Not Known	Aseptic meningitis, headache, dizziness
Cardiac Disorders	Not Known	Cardiac failure, oedema
Vascular Disorders	Not Known	Hypertension
Respiratory, Thoracic and Mediastinal Disorders	Not Known	Bronchospasm, asthma, dyspnoea, rhinitis
Gastrointestinal Disorders	Not Known	Gastrointestinal haemorrhage, gastrointestinal disturbances, peptic ulcer, melaena, haematemesis, mouth ulceration
Hepatobiliary Disorders	Not Known	Transient hepatic impairment with increase in liver transaminases
Skin and Subcutaneous Tissue Disorders	Not Known	Stevens-Johnson syndrome, toxic epidermal necrolysis, rash
	Not Known	Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)
Renal and Urinary Disorders	Not Known	Blood uric acid increased
Investigations	Not Known	Bleeding time prolonged, platelet adhesiveness decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose

Salicylate poisoning is usually associated with plasma concentrations > 350 mg/L (2.5 mmol/L). Most

deaths in adults occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms

These include dizziness, tinnitus, dehydration, vertigo, deafness, warm extremities with bounding pulses, increased respiratory rate and depth, sweating, nausea, vomiting, altered glucose metabolism, mental confusion, hyperventilation, respiratory alkalosis, metabolic acidosis, ketosis, and fluid and electrolyte losses. Some degree of acid-base disturbance is present in most cases.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions may occur and are more common in children than in adults.

In children serious signs of overdosage may develop rapidly.

Management of overdosage:

Treatment is symptomatic and supportive: the serum salicylate levels should be closely monitored and forced alkaline diuresis instituted if appropriate.

Restoration of fluid, electrolyte and acid balance, dialysis and supportive therapy may be required.

Adult presenting within one hour of ingestion of more than 250 mg/kg should be given activated charcoal.

Elimination is increased by urinary alkalinisation. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8,4 % sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylic excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700mg/L (5.1 mmol/L) or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.8 Non-narcotic analgesics, antipyretics.

Pharmacotherapeutic group: Other analgesics and antipyretics: ATC Code: N02BA01

Aspirin has analgesic, anti-pyretic and anti-inflammatory actions. Aspirin inhibits the biosynthesis of prostaglandins. Aspirin inhibits the cyclo-oxygenase enzyme involved in conversion of phospholipids to prostaglandins and its effects on the body are believed to result primarily from prevention of prostaglandin production. These effects include peripheral analgesia, fever reduction, reduction in irreversible inflammation and inhibition of platelet aggregation.

Experimental data suggest that NSAIDs may inhibit the effect of aspirin on platelet aggregation when they are dosed concomitantly.

5.2 Pharmacokinetic properties

Absorption: Aspirin is rapidly absorbed from the stomach and upper gastrointestinal tract. It is subject to first-pass metabolism with an overall bioavailability of around 70%.

Biotransformation: Metabolism is by conversion to salicylic acid and then by further conversion to other metabolites. These are excreted by the kidneys in both free and conjugated form. The plasma half-life of aspirin is around 15- 20 minutes and that of salicylic acid is 2-3 hours.

5.3 Preclinical safety data

No preclinical findings of relevance have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Maize starch

Microcrystalline cellulose

Purified talc

Lemon flavour 51124

Saccharin (sweetener)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

6.5 Nature and contents of container

Packs of 8 and 32 tablets in foil.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Reckitt Benckiser Pharmaceuticals (Pty) Ltd

8 Jet Park Road

Elandsfontein

1601

8. REGISTRATION NUMBER

R/2.8/99

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date on the registration certificate of DISPRIN MELTS: 15/05/1984

10. DATE OF REVISION OF THE TEXT

Applicant: Reckitt Benckiser Pharmaceuticals (Pty) Ltd
Product: Disprin Melts
Dosage: Tablets
Strength: 300 mg aspirin
PI Safety Update approval: 06 Feb 2024

Date of the most recently revised package insert as approved by council: 06/02/2024