Professional information for BENYLIN FOUR FLU TABLETS

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

BENYLIN FOUR FLU TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Diphenhydramine hydrochloride	12,5 mg
Pseudoephedrine hydrochloride	22,5 mg
Paracetamol	500,0 mg

Excipients with known effect:

Contains Sunset Yellow FCF (E110).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Orange, oval, biconvex film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms associated with colds and flu; including coughing, fever, headache, minor aches and pains and nasal congestion.

4.2 Posology and method of administration

Adults, the elderly and children 12 years and older:

Two tablets four times daily. Do not exceed 8 tablets in 24 hours.

Children aged 6 to less than 12 years:

One tablet four times daily. Do not exceed 4 tablets in 24 hours.

Children under 6 years:

Not recommended.

For oral use only.

Hepatic dysfunction

Caution should be exercised when administrating BENYLIN FOUR FLU TABLETS to patients with severe hepatic impairment.

Renal dysfunction

Caution should be exercised when administering BENYLIN FOUR FLU TABLETS to patients with moderate to severe renal impairment.

4.3 Contraindications

- Hypersensitivity to diphenhydramine hydrochloride, pseudoephedrine hydrochloride, paracetamol or to any of the other ingredients in BENYLIN FOUR FLU TABLETS (see section 6.1)
- Most types of cardiovascular disease, including angina and hypertension
- Hyperthyroidism

- Hyperexcitability
- Phaeochromocytoma
- Closed angle glaucoma
- Concomitant use of monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping treatment with this class of medicine. The concomitant use of these medications may cause a rise in blood pressure and/or hypertensive crisis (see section 4.5).
- Severe liver disease.
- Should be avoided in patients undergoing anaesthesia with cyclopropane, halothane, or other halogenated anaesthetics.

4.4 Special warnings and precautions for use

BENYLIN FOUR FLU TABLETS contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

Patients with the following conditions should be advised to consult a doctor before using BENYLIN FOUR FLU TABLETS: a respiratory condition, such as emphysema, chronic bronchitis, or acute or chronic bronchial asthma, or prostate hyperplasia with urinary retention.
BENYLIN FOUR FLU TABLETS may cause urinary retention in patients with prostatic hypertrophy.

BENYLIN FOUR FLU TABLETS should not be used continuously for more than ten days; if symptoms persist, irrespective of therapy used, a doctor should be consulted. Dosages in excess of those recommended may cause severe liver or kidney damage.
BENYLIN FOUR FLU TABLETS may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressant

medicines (such as sedatives and tranquilisers). While taking BENYLIN FOUR FLU TABLETS, patients should avoid alcoholic beverages and consult with a health care provider prior to taking with central nervous system depressants.

Chronic alcohol users should ask their doctor whether they should take paracetamol or other analgesics or antipyretics.

BENYLIN FOUR FLU TABLETS should not be taken without consulting a doctor or pharmacist if a patient is presently taking other medicines for depression, psychiatric or emotional conditions or hypertension (see section 4.5).

Not to be taken with any other paracetamol or diphenhydramine-containing products, even ones used on skin.

In infants and children BENYLIN FOUR FLU TABLETS may act as a cerebral stimulant. Symptoms of stimulation include insomnia, nervousness, tachycardia, tremors and convulsions.

Large doses may precipitate fits in epileptics. Deepening coma, extrapyramidal effects and photosensitisation of the skin may occur.

Elderly patients are more susceptible to the central nervous system depressant and hypotensive effects.
The positive results of skin tests may be suppressed.

Patients with impaired kidney or liver function should take BENYLIN FOUR FLU TABLETS under medical supervision only.

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions and the use of BENYLIN FOUR FLU TABLETS should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

BENYLIN FOUR FLU TABLETS should not be used by patients with renal disease or diabetes.

Taking more than the recommended dose (overdose) may result in liver damage. In case of overdose, get medical help immediately. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

There have been reports of ischaemic colitis with pseudoephedrine. BENYLIN FOUR FLU TABLETS should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop (see section 4.8).

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) have been reported very rarely with pseudoephedrine-containing products, such as BENYLIN FOUR FLU TABLETS. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localised on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as formation of small pustules occur, with or without pyrexia or erythema, then treatment with BENYLIN FOUR FLU TABLETS should be discontinued and a doctor should be consulted (see section 4.8).

Patients should not use BENYLIN FOUR FLU TABLETS for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a doctor.

4.5 Interaction with other medicines and other forms of interaction

Warfarin-like compounds

For most patients, occasional use of paracetamol generally has little or no effect on the International Normalised Ratio (INR) in patients on chronic warfarin therapy; however, there has been controversy regarding the possibility of paracetamol potentiating the anticoagulant effects of warfarin and other coumarin derivatives. Patients should consult a doctor or pharmacist before use if they are taking warfarin or other coumarin derivatives.

Central nervous system (CNS) depressants (alcohol, sedatives, tranquilisers)

Diphenhydramine may potentiate the effects of other CNS depressants such as anti-depressants, minor tranquillisers, neuroleptics, barbiturates and alcohol, and other medicines with anti-cholinergic properties such as tricyclic anti-depressants.

Antihypertensive medicines, sympathomimetic medicines and MAOIs

Pseudoephedrine may reverse the effect of antihypertensive medicines which modify sympathetic activity, and concomitant use with other sympathomimetic medicines such as decongestants, tricyclic anti-depressants and appetite suppressants or with monoamine oxidase inhibitors, which interfere with the catabolism of sympathomimetic amines, may cause a rise in blood pressure.

Cardiac glycosides, quinidine and tricyclic anti-depressants

An increased risk of dysrhythmias may also occur if sympathomimetic medicines are given to patients receiving cardiac glycosides, quinidine, or tricyclic anti-depressants.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Diphenhydramine

Diphenhydramine crosses the placenta and is excreted into breast milk, but levels have not been reported.

Paracetamol

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol *in utero* show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Pseudoephedrine

Pseudoephedrine distributes into and is concentrated in breast milk. Up to 0,7 % of a single 60 mg dose of pseudoephedrine may be distributed into breast milk over 24 hours. Pseudoephedrine concentrations in milk are from 2 to 3 fold higher than those in plasma. This milk/plasma medicine concentration profile suggests low protein binding, although no protein plasma binding data in humans are available. Data from a study of lactating mothers taking 60 mg pseudoephedrine every 6 hours suggests that from 2,2 to 6,7 % of the maximum daily dose (240 mg) may be available to the infant from a breastfeeding mother.

4.7 Effects on ability to drive and use machines

BENYLIN FOUR FLU TABLETS can cause side effects such as sedation, drowsiness, dizziness or blurred vision. Patients should be warned not to drive a motor vehicle, operate dangerous machinery, or climb dangerous heights, as impaired decision making could lead to accidents.

4.8 Undesirable effects

Diphenhydramine hydrochloride:

Blood and the lymphatic system disorders:

Less frequent: blood dyscrasias (including agranulocytosis, leucopenia and haemolytic anaemia), thrombocytopenia

Immune system disorders:

Less frequent: allergic reactions and anaphylaxis

Metabolism and nutrition disorders:

Less frequent: anorexia or increased appetite

Psychiatric disorders:

Less frequent: euphoria

Nervous system disorders:

Frequent: sedation (varying from slight drowsiness to deep sleep), lassitude, dizziness, incoordination, headache

Eye disorders:

Less frequent: blurred vision

Ear and labyrinth disorders:

Less frequent: tinnitus

Vascular disorders:

Less frequent: hypotension

Respiratory, thoracic and mediastinal disorders:

Less frequent: tightness of the chest

Gastrointestinal disorders:

Less frequent: nausea, vomiting, diarrhoea, constipation, epigastric pain and dryness of the mouth

Musculoskeletal, connective tissue and bone disorders:

Less frequent: muscular weakness

Renal and urinary disorders:

Less frequent: difficulty in micturition, dysuria

Paracetamol:

Blood and the lymphatic system disorders:

Less frequent: neutropenia, pancytopenia, leucopenia, agranulocytosis, thrombocytopenia

Immune system disorders:

Less frequent: sensitivity reactions resulting in skin rash*, laryngeal oedema, angioedema and anaphylaxis

* (The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by fever and mucosal lesions.)

Endocrine disorders:

Less frequent: pancreatitis

Pseudoephedrine hydrochloride:

Metabolism and nutrition disorders:

Less frequent: altered metabolism (including changes in blood sugar levels)

Frequency unknown: hypokalaemia

Psychiatric disorders:

Less frequent: fear, anxiety, restlessness, insomnia, confusion, irritability, and psychotic states

Nervous system disorders:

Less frequent: tremor, headache

Cardiac disorders:

Less frequent: pulmonary oedema, reflex bradycardia, tachycardia and cardiac dysrhythmias, anginal pain, palpitations, and cardiac arrest

Vascular disorders:

Less frequent: hypertension, cerebral haemorrhage, hypotension (with dizziness), fainting, flushing

Respiratory, thoracic and mediastinal disorders:

Less frequent: dyspnoea

Gastrointestinal disorders:

Less frequent: reduced appetite, nausea, vomiting, hypersalivation

Skin and subcutaneous tissue disorders:

Less frequent: sweating

Renal and urinary disorders:

Less frequent: difficulty in micturition and urinary retention

General disorders and administrative site conditions:

Less frequent: weakness.

Post-marketing experience:

Blood and the lymphatic system disorders:

Less frequent: blood disorders, blood dyscrasias (including thrombocytopenia and agranulocytosis) following paracetamol use

Immune system disorders:

Less frequent: anaphylactic reaction, hypersensitivity (cross-sensitivity may occur with other sympathomimetics)

Psychiatric disorders:

Frequent: insomnia, nervousness

Less frequent: anxiety, confusional state, euphoric mood, hallucination, visual hallucination), irritability, restlessness, depression, sleep disorder

Frequency unknown: excitability, paranoid delusions

Nervous system disorders:

Frequent: headache, somnolence, dizziness, sedation, paradoxical stimulation, psychomotor impairment

Less frequent: agitation, cerebrovascular accident, convulsions, abnormal coordination, paraesthesia, psychomotor hyperactivity, tremor, extrapyramidal disorder

Frequency unknown: posterior reversible encephalopathy syndrome (PRES)/reversible cerebral vasoconstriction syndrome (RCVS)

Eye disorders:

Frequent: blurred vision

Ear and labyrinth disorders:

Less frequent: tinnitus

Cardiac disorders:

Less frequent: dysrhythmia, myocardial infarction palpitations, tachycardia, cardiac arrest

Frequency unknown: myocardial ischaemia

Vascular disorders:

Less frequent: hypotension

Frequency unknown: hypertension

Respiratory, thoracic and mediastinal disorders:

Frequent: increased viscosity of bronchial secretions

Less frequent: chest discomfort, dry throat, dyspnoea, nasal dryness

Gastrointestinal disorders:

Frequent: dry mouth, nausea, gastrointestinal disorder

Less frequent: abdominal pain, ischaemic colitis, constipation, diarrhoea, dyspepsia, vomiting

Hepatobiliary disorders:

Less frequent: liver disorder

Skin and subcutaneous tissue disorders:

Less frequent: acute generalised exanthematous pustulosis (AGEP), angioedema, fixed eruption, pruritus, rash, pruritic rash, urticaria

Frequency unknown: erythema

Renal and urinary disorders:

Frequent: urinary retention

Less frequent: dysuria

General disorders and administration site conditions:

Frequent: asthenia

Investigations:

Less frequent: increased transaminase, increased blood pressure

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of BENYLIN FOUR FLU TABLETS is important. It allows continued monitoring of the benefit/risk balance of BENYLIN FOUR FLU TABLETS. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.
For further information, please contact the Johnson & Johnson call centre on 0860 410032 (landline).

4.9 Overdose

Diphenhydramine hydrochloride:

Overdosage may be fatal especially in infants and children.

In infants & children CNS stimulation predominates over CNS depression causing ataxia, excitement, tremors, psychoses, hallucinations and convulsions; hyperpyrexia may also occur. Deepening coma and cardio-respiratory collapse may follow. In adults, CNS depression with drowsiness, coma and convulsions, progressing to respiratory failure or possibly cardiovascular collapse.

Paracetamol:

Nausea, vomiting and anorexia. Liver damage which may be fatal, may only appear after a few days. Acute intoxication may cause kidney failure.

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5-10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.
Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage.
Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.
Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur.
Cardiac dysrhythmias have been reported.

Treatment for paracetamol overdosage:

Any adult person who has had about 7,5 grams of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube.

Ingestion of amounts of paracetamol smaller than this may require treatment in patients

susceptible to paracetamol poisoning (see above). In patients who are stuporous or comatose, endotracheal intubation should precede gastric lavage in order to avoid aspiration.

***N*-acetylcysteine** should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

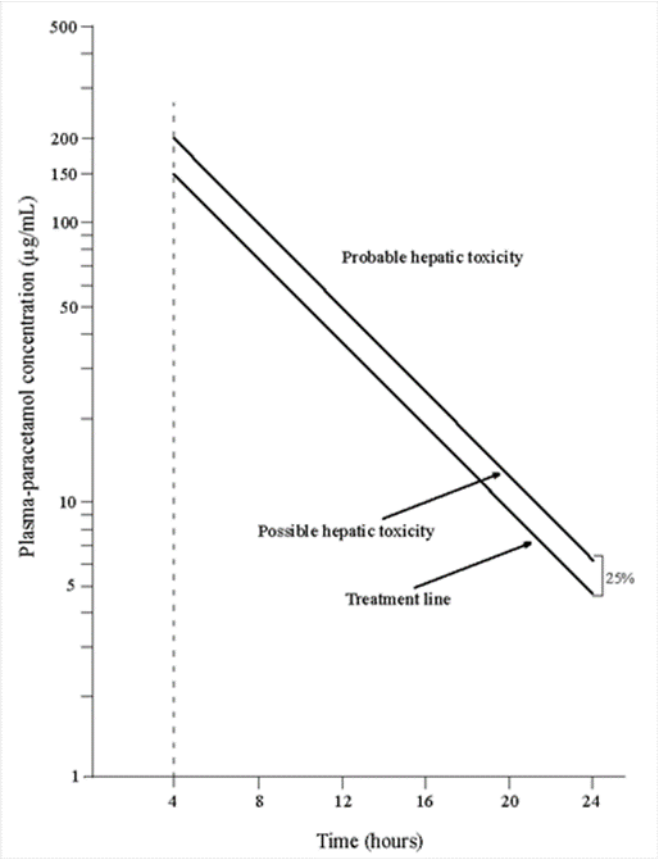
An initial dose of 150 mg/kg *N*-acetylcysteine in 200 mL glucose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL glucose injection over the next four hours, and then 100 mg/kg in 1000 mL glucose injection over the next sixteen hours.

The volume of intravenous fluid should be modified for children.

Orally (not the treatment of choice): 140 mg/kg as a 5 % solution initially, followed by 70 mg/kg every four hours for seventeen doses. *N*-acetylcysteine is more likely to be effective if administered within 8 hours of overdosage.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage.

Levels done before four hours, unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with *N*-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



Source: Martindale, The Complete Drug Reference, Paracetamol, Online Edition, 3rd Quarter 2020.

Those whose plasma paracetamol levels are above the “normal treatment line", should continue *N*-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “treatment line". Prothrombin index correlates best with survival.

If *N*-acetylcysteine is not available, methionine 2,5 gram may be given immediately, followed by 2,5 g every four hours for three doses. Patients should however preferably be transferred to a facility where *N*-acetylcysteine can be given.

Monitor all patients with significant ingestions for at least ninety six hours.

Pseudoephedrine hydrochloride:

Convulsions and hyperpyrexia in children due to cerebral stimulation. In adults symptoms of stimulation include insomnia, nervousness, tachycardia, tremors, muscle twitching and convulsions.

Treatment:

Symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

A 5.8 Preparations for the common cold including nasal decongestants and antihistaminics.

Pharmacotherapeutic group: Other analgesics and antipyretics; Paracetamol, combinations excluding psycholeptics.

ATC code: N02BE51.

Diphenhydramine hydrochloride has an antihistaminic action.

Paracetamol has central analgesic and antipyretic actions and pseudoephedrine hydrochloride is an indirectly acting sympathomimetic which has vasoconstrictor, bronchodilator and decongestant effects.

5.2 Pharmacokinetic properties

Diphenhydramine

Diphenhydramine is well absorbed after oral administration with peak plasma levels at 2,5 hours and is subject to extensive first pass metabolism. Diphenhydramine is 75 % bound to plasma proteins, but binding decreases with chronic liver disease. Metabolism is by 2 successive *N*-

demethylations followed by oxidation to a carboxylic acid. The terminal half life lies between 3,4 and 9,3 hours.

Paracetamol

Paracetamol is rapidly and completely absorbed with peak plasma levels seen within 30 to 60 minutes. Less than 50 % is protein bound and paracetamol is uniformly distributed throughout the body fluids. Paracetamol is eliminated by metabolism to inactive conjugates followed by urinary excretion. The half-life is 2,75 – 3,25 hours.

Pseudoephedrine

Pseudoephedrine is rapidly absorbed, with peak serum levels after approximately 2.6 hours and onset of effect within about 30 minutes. It is well distributed throughout body fluids and tissues. Approximately 50 % of the medicine is excreted unchanged, the remainder undergoes metabolism to inactive metabolites. About 6 % is converted to the active metabolite norpseudoephedrine.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Crospovidone (E1202)

Magnesium stearate (E572)

Microcrystalline cellulose (E460(i))

Opadry Yellow (colourant, containing hypromellose (E464),

macrogol 6000 (E1521), Sunset Yellow FCF (E110), talc (E553b), titanium dioxide (E171) and quinoline yellow aluminium lake)

Povidone (E1201)

Pregelatinised maize starch

Stearic acid (E570).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25℃.

Store in a dry place, protected from light.

Keep in the original container until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Opaque white PVC blister packs containing 24 tablets packed into a carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Johnson & Johnson (Pty) Ltd.

241 Main Road

Retreat

7945

South Africa

8. REGISTRATION NUMBER

33/5.8/0509

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 September 2004.

10. DATE OF REVISION OF THE TEXT

1 March 2022.

EXPORT REGISTRATION DETAILS:	
Namibia:	06/5.8/0251
Mauritius:	R3650/02/14