Professional information for BENYLIN® FOUR FLU LIQUID

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE

BENYLIN® FOUR FLU LIQUID

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL of liquid contains:

Diphenhydramine hydrochloride	25,0 mg
Pseudoephedrine hydrochloride	45,0 mg
Paracetamol	1 000,0 mg
Excipients with known effect:	
Preservative: Sodium benzoate	0,2 % *m/v*
Alcohol	9,9 % *v/v*

Contains sweetener: Each 20 mL contains 112 mg saccharin sodium.

Sugar free.

3. PHARMACEUTICAL FORM

Oral liquid.

A clear, orange liquid with a characteristic honey and lemon odour and taste.

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

DO NOT EXCEED THE RECOMMENDED DOSE.

For oral use only.

Shake the bottle before use.

Adults, the elderly and children over 12 years

20 mL (four 5 mL medicine measurements) four times daily as required. Do not take more frequently than every four hours.

Maximum daily dose: Do not exceed four doses in 24 hours.

Children under 12 years of age: Not recommended.

4.3 Contraindications

- Known hypersensitivity to diphenhydramine hydrochloride, pseudoephedrine hydrochloride, paracetamol or any of the other ingredients (see section 6.1).
- Most types of cardiovascular disease, including angina and hypertension and also in hyperthyroidism, hyperexcitability, phaeochromocytoma and closed angle glaucoma.
- Concomitant use of monoamine oxidase inhibitors, or within 14 days of stopping treatment with this class of medicine.

  Concomitant use may cause a rise in blood pressure and/or hypertensive crisis.
- Severe liver disease.
- Should be avoided in patients undergoing anaesthesia with cyclopropane, halothane, or other halogenated anaesthetics.
- Not recommended for children under the age of 12 years.

4.4 Special warnings and precautions for use

BENYLIN® FOUR FLU LIQUID 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.

BENYLIN® FOUR FLU LIQUID should not be used continuously for more than ten days; if symptoms persist, irrespective of therapy used, a medical practitioner should be consulted. Dosages in excess of those recommended may cause severe liver or kidney damage (see section 4.9).

BENYLIN® FOUR FLU LIQUID may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol, sedatives, tranquilisers or other central nervous system depressants.
The use of alcohol while using BENYLIN® FOUR FLU LIQUID should be avoided.

BENYLIN® FOUR FLU LIQUID should not be used without consulting a doctor or pharmacist if the patient is presently taking monoamine oxidase inhibitors (see section 4.3) or other medicines for depression, psychiatric or emotional conditions or hypertension (see section 4.5).

A medical practitioner should be consulted if there is a pre-existing respiratory disease such as emphysema, chronic bronchitis, acute or chronic bronchial asthma or glaucoma.
Patients should not use BENYLIN® FOUR FLU LIQUID for persistent or chronic cough, such as occur with asthma, or where cough is accompanied by excessive secretions, unless directed by a medical practitioner.
BENYLIN® FOUR FLU LIQUID should not be taken with any other pseudoephedrine, paracetamol-containing products, or with any other product containing diphenhydramine hydrochloride, even if used on skin.

As both diphenhydramine hydrochloride and pseudoephedrine hydrochloride have been associated with central nervous system adverse events, there is a possibility that the risk of experiencing such adverse events may be increased by use of the combination.
If hallucinations, restlessness and sleep disturbances occur, stop using BENYLIN® FOUR FLU LIQUID.

Patients with difficulty in urination due to enlargement of the prostate gland, should be advised to consult their medical practitioner before using diphenhydramine or pseudoephedrine containing medicines.

Chronic alcohol abusers should ask their medical practitioners whether they should take paracetamol or other pain relievers or fever reducing medication.

Patients with hepatic disease should consult a medical practitioner before using BENYLIN® FOUR FLU LIQUID (see section 4.3).

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions, and use of BENYLIN® FOUR FLU LIQUID should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.
Use with care in patients with pre-existing cardiovascular disease in particular those with coronary heart disease and hypertension (see section 4.3).

Patients with thyroid disease, diabetes mellitus or decreased kidney function should not use pseudoephedrine hydrochloride unless advised by a medical practitioner.

There have been reports of ischaemic colitis with pseudoephedrine. BENYLIN® FOUR FLU LIQUID should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) have been reported very rarely with pseudoephedrine containing products. 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 LIQUID should be discontinued and a doctor should be consulted.

If symptoms persists or gets worse, or if new symptoms occur, a doctor should be consulted.

BENYLIN® FOUR FLU LIQUID contains sodium benzoate

An increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

4.5 Interaction with other medicines and other forms of interaction

Central nervous system depressants: Diphenhydramine hydrochloride may enhance the sedative effects of central nervous system depressants, including alcohol, tranquilisers, neuroleptic medicines, barbiturates and sedatives.

Antimuscarinic medicines (having anti-cholinergic properties): Diphenhydramine hydrochloride may have an additive effect with medicines such as atropine, tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) (see section 4.3).

Antibacterial medicines: Diphenhydramine hydrochloride may mask the damage caused by ototoxic medicines such as aminoglycosides.

Cough and cold preparations: Avoid concurrent use as other preparations could have similar acting components which will result in a potentiation of the effect of both products.

Laboratory tests: Diphenhydramine hydrochloride may suppress cutaneous histamine response to allergen.

Antihypertensive medicines: Pseudoephedrine hydrochloride may reverse the effect of antihypertensive medicines which modify sympathetic activity.

Sympathomimetic medicines: Concomitant use with other sympathomimetic medicines such as decongestants, tricyclic anti-depressants and appetite suppressants or with monoamine oxidase inhibitors, including linezolid which interfere with the catabolism of sympathomimetic amines may cause a rise in blood pressure.

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

Anticoagulant medicines: Paracetamol may potentiate the anticoagulant effects of warfarin and other coumarin derivatives.

Hepatotoxic medicines: The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes.

Metoclopramide: May accelerate the absorption of paracetamol.

Probenecid: Paracetamol excretion may be affected and plasma concentrations altered when given together with probenecid.

Cholestyramine: Reduces the absorption of paracetamol if given within 1 hour of paracetamol.

4.6 Fertility, pregnancy and lactation

The safety of BENYLIN® FOUR FLU LIQUID in pregnancy and lactation has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

BENYLIN® FOUR FLU LIQUID may lead to prolonged drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants.

Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration 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, anaphylaxis

Psychiatric disorders:

Frequency unknown: euphoria.

Nervous system disorders:

Frequent: sedation (varying from slight drowsiness to deep sleep), lassitude, dizziness, inco-ordination.

Less frequent: deepening coma, extrapyramidal effects.

Frequency unknown: headache

Elderly patients are more susceptible to the central nervous system depressant effects.

In infants and children it may act as a cerebral stimulant.

Symptoms of stimulation include insomnia, nervousness, tachycardia, tremors and convulsions.

Large doses may precipitate fits in epileptics.

Eye disorders:

Frequency unknown: blurred vision

Ear and labyrinth disorders:

Frequency unknown: tinnitus

Vascular disorders:

Less frequent: hypotension

Elderly patients are more susceptible to the hypotensive effects.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: tightness of the chest

Gastrointestinal disorders:

Less frequent: nausea, vomiting, diarrhoea, constipation, anorexia or increased appetite, epigastric pain

Frequency unknown: dryness of the mouth

Skin and subcutaneous tissue disorders:

Less frequent: photosensitisation of the skin

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: muscular weakness

Renal and urinary disorders:

Frequency unknown: difficulty in micturition, dysuria

Investigations:

Less frequent: The positive results of skin tests may be suppressed

Paracetamol

Blood and the lymphatic system disorders:

Less frequent: neutropenia, pancytopenia, leucopenia, 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:

Frequency unknown: pancreatitis

Pseudoephedrine hydrochloride

Metabolism and nutrition disorders:

Less frequent: hypokalaemia

Frequency unknown: altered metabolism (including changes in blood sugar levels)

Psychiatric disorders:

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

Nervous system disorders:

Less frequent: headache

Cardiac disorders:

Less frequent: pulmonary oedema, reflex bradycardia, tachycardia, cardiac dysrhythmias, anginal pain, palpitations, 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, hypersalivation, nausea and vomiting

Skin and subcutaneous tissue disorders:

Less frequent: sweating

Renal and urinary disorders:

Less frequent: difficulty in micturition and urinary retention (in patients with prostatic hypertrophy)

General disorders and administrative site conditions:

Less frequent: weakness

Post-marketing data

The side effects reported are:

Psychiatric disorders

Hallucinations (including visual hallucinations), depression**,** excitability and paranoid delusions.

Nervous system disorders

Paradoxical stimulation, agitation, paraesthesia, psychomotor hyperactivity, cerebrovascular accident.

Cardiac disorders

Myocardial infarction.

Respiratory, thoracic and mediastinal disorders

Dry throat, nasal dryness, thickened respiratory tract secretions.

Gastrointestinal disorders

Abdominal pain, dyspepsia, ischaemic colitis.

Skin and subcutaneous tissue disorders

Pruritus, pruritic rash, acute generalised exanthematous pustulosis, fixed eruption.

General disorders and administrative site conditions

Jittery feeling.

Investigations

Increased transaminases.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of BENYLIN FOUR FLU LIQUID is important. It allows continued monitoring of the benefit/risk balance of BENYLIN FOUR FLU LIQUID. Healthcare 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:

Mild to moderate symptoms are:

Somnolence, anticholinergic syndrome (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds, tachycardia, mild hypertension, nausea and vomiting are common after overdose. Agitation, confusion and hallucinations may develop with moderate poisoning.

Severe symptoms:

Effects may include delirium, psychosis, seizures, coma, convulsions, hypotension, QRS widening, and ventricular dysrhythmias, including torsades de pointes, but are generally reported in adults after large ingestions. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma or seizures. Death may occur as a result of respiratory failure or circulatory collapse.

Paracetamol

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

Although evidence is limited it is recommended that any adult person who has ingested 5 – 10 grams or more 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 dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 m mL dextrose injection over the next four hours, and then 100 mg/kg in 1 000 mL dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children.**
Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.
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.

Figure 1: A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion (Source: Martindale, The Complete Drug Reference).

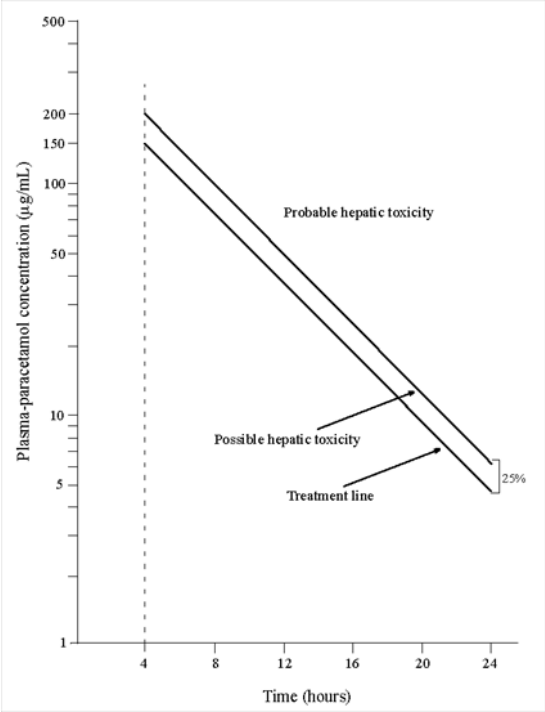

Figure 1: Adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. Pediatrics 1975; 55: 871–6.

Notes for the use of this chart (figure 1):

1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.

4. The solid line 25 % below the standard nomogram is included to allow for possible errors in plasma assays and estimated time from ingestion of an overdose. Patients whose plasma-paracetamol concentrations are on or above this line should be treated.
5. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

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 “high risk treatment line”. Prothrombin index correlates best with survival.

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

Pseudoephedrine hydrochloride

Overdosage may result in nausea, vomiting, sympathomimetic symptoms including central nervous system stimulation, insomnia, tremor, mydriasis, anxiety, agitation, hallucinations, seizures, palpitations, tachycardia, hypertension, and reflex bradycardia. Other effects may include dysrhythmias, hypertensive crisis, intracerebral haemorrhage, myocardial infarction, psychoses, rhabdomyolysis, hypokalaemia, and ischemic bowel infarction. Drowsiness has been reported with overdose in children.

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 a potent 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 hydrochloride

Diphenhydramine hydrochloride, an antihistamine, is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations occur about 1 to 4 hours after oral doses. Diphenhydramine hydrochloride is widely distributed throughout the body including the central nervous system. It crosses the placenta and appears in breast milk. Diphenhydramine hydrochloride is highly bound to plasma proteins. Metabolism is extensive.

Diphenhydramine hydrochloride is excreted mainly in the urine as metabolites; little is excreted as unchanged molecule. The elimination half-life has been reported to range from 2,4 to 9,3 hours.

Paracetamol

Paracetamol is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 10 to 60 minutes after oral dosing. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.

Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5 % is excreted as unchanged paracetamol. A minor hydroxylated metabolite (*N*-acetyl-*p*-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

Pseudoephedrine hydrochloride

Pseudoephedrine hydrochloride is readily absorbed from the gastrointestinal tract. It is excreted largely unchanged in the urine with small amounts of its hepatic metabolite. It has a half-life of about 5 to 8 hours; elimination is enhanced and half-life accordingly shorter in acid urine. Pseudoephedrine hydrochloride is distributed into breast milk.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients are:

citric acid (E331),

colourants (D & C Yellow No. 10, patent blue V and Ponceau 4R),

denatured alcohol menthol,

flavourants (milk cream, eucalyptol, honey, lemon, and menthol),

glycerol (E422),

polyethylene glycol (E1521),

propylene glycol (E1520),

purified water,

sodium benzoate (E211),

sodium carboxymethylcellulose (E466),

sodium citrate (E331), and

sodium saccharin (E954).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 ˚C.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Round, amber glass bottle of 100 and 200 mL, with a plastic measuring cup.

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

33/5.8/0345

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 October 2000

10. DATE OF REVISION OF THE TEXT

30 May 2024.

EXPORT REGISTRATION DETAILS

Botswana:	BOT 0500811	Kenya:	H2002/240
Malawi:	PMPB/PL 353/6	Mozambique	944
Namibia:	04/5.8/1528 NS1		
Nigeria:	NAFDAC Reg. No. B4-9043		
Tanzania:	TAN 00,2219 R05A WAR	Uganda:	4010/25/01
Zambia:	082/048 POM	Zimbabwe:	2008/22.2.5/4515 P