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SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE

COLCAPS ® CHILDREN'S SYRUP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 5 ml contains:	
Codeine phosphate	5 mg
Promethazine hydrochloride	6,5 mg
Pseudoephedrine hydrochloride	25 mg
Paracetamol	120 mg

Contains Preservatives:

Methyl hydroxybenzoate	0,06 % $^{m}/_{v}$
Propyl hydroxybenzoate	0,03 % $^{m}/_{v}$

Contains Alcohol: 10,0 % $^{v}/_{v}$

Contains Antioxidants: Ascorbic acid 100 mg and Citric acid 1,1 mg.

Contains sugar: Sucrose 2,0 g; Liquid Glucose 2,2 g;

Contains sweeteners: Sodium Cyclamate 15,4 mg and saccharin sodium 4,4 mg.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

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Syrup.

Dark brown liquid with an odour and taste of alcohol and raspberry.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

The symptomatic relief of colds and flu associated with cough in children 2 years and older.

4.2 Posology and method of administration

DO NOT EXCEED THE RECOMMENDED DOSE.

2 years - 5 years: 5 ml (1 teaspoonful) three times a day.

5 years - 12 years: 5 ml or 10 ml (1 or 2 teaspoonfuls) three times a day.

Not recommended for use in children under 2 years of age (see Section 4.3 Contraindications).

4.3 Contraindications:

COLCAPS CHILDREN'S SYRUP is contraindicated in:

- Known hypersensitivity to the active substances or to any of the excipients listed under Section 6.1.
- Severe liver and renal function impairment.
- Patients receiving monoamine oxidase inhibitor treatment, or within 14 days of such treatment (see section 4.4 Special Warnings and precautions for use).
- Children under 2 years of age
- Breastfeeding mothers (See Section 4.6)

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- CYP2D6 ultra-rapid metabolisers who convert codeine into its active metabolite more rapidly and completely than other people. These individuals may experience signs of overdose/toxicity including symptoms such as extreme sleepiness, confusion, or shallow breathing, which may be life threatening. (see section 4.4 and section 5.2)
- Acute respiratory depression and obstructive airways disease especially in the presence of cyanosis and excessive bronchial secretion, and after operations on the biliary-tract.
- Patients at risk of paralytic ileus.
- Convulsive disorders, head injuries, and conditions in which intracranial pressure is raised.
- Acute alcoholism
- COLCAPS CHILDREN'S SYRUP should not be given during an attack of bronchial asthma or in heart disease.
- The use of promethazine as contained in COLCAPS CHILDREN'S SYRUP may be associated with the sudden infant death syndrome.

4.4 Special warnings and precautions for use

Glucose:

- COLCAPS CHILDRENS SYRUP contains liquid glucose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Sucrose:

- COLCAPS CHILDRENS SYRUP contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.
- Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase- isomaltase insufficiency should not take

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COLCAPS CHILDRENS SYRUP.

Paracetamol:

- Do not use continuously for more than ten days without consulting your doctor.
- Patients suffering from liver or kidney disease should take paracetamol-containing preparations such as COLCAPS CHILDREN'S SYRUP under medical supervision. Dosage in excess of those recommended may cause severe liver damage.

COLCAPS CHILDREN'S SYRUP 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, poison control centre must be contacted immediately.

- Patients suffering from hepatitis or alcoholism or recovering from any form of liver disease should not take excessive quantities of COLCAPS CHILDREN'S SYRUP.
- COLCAPS CHILDREN'S SYRUP should be used with caution in patients with hyperthyroidism; cardiovascular disease such as dysrhythmia or tachycardia; occlusive vascular disorders, including arteriosclerosis, hypertension or aneurysms; diabetes mellitus and closed angle glaucoma.
- COLCAPS CHILDREN'S SYRUP should not be used by patients being treated with monoamine oxidase inhibitors (MAOIs), anti-depressants or anxiolytics or within two weeks of stopping treatment with these medications (see section 4.3 Contraindications).

Codeine phosphate:

- Codeine should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, impaired liver function, ~~prostatic hypertrophy~~ or shock.
- Codeine should be used with caution in patients with inflammatory or obstructive bowel disorders.

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- Codeine should be given with caution to patients with myasthenia gravis.
- Exceeding the prescribed dose, together with prolonged and continuous use of this medicine, may lead to dependency and addiction.

Promethazine hydrochloride:

- Promethazine hydrochloride has anticholinergic properties and should be used with care in conditions such as glaucoma.
- Cases of respiratory depression, including fatalities have been reported in children under two years of age.
- Promethazine hydrochloride may thicken or dry lung secretions and impair expectoration. It should therefore be used with caution in patients with asthma, bronchitis or bronchiectasis.
- Use with care in patients with severe coronary artery disease, narrow angle glaucoma, epilepsy or hepatic and renal insufficiency.
- Caution should be exercised in patients with bladder neck or pyloro-duodenal obstruction.
- The use of promethazine hydrochloride should be avoided in children and adolescents with signs and symptoms suggestive of Reye's Syndrome.
- Promethazine hydrochloride may mask the warning signs of ototoxicity caused by ototoxic medicines e.g. salicylates.
- Promethazine hydrochloride may also delay the early diagnosis of intestinal obstruction or raised intracranial pressure through the suppression of vomiting.

Pseudoephedrine hydrochloride:

- Use with caution in occlusive vascular disease.
- COLCAPS CHILDREN’S SYRUP should be discontinued if hallucinations or restlessness occur.

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4.5 Interaction with other medicines and other forms of interaction

Interactions with other medicines

- The depressant effects of *codeine* are enhanced by depressants of the central nervous system such as *alcohol, anaesthetics, hypnotics, sedatives*, and *phenothiazines*.
- The actions of *codeine* may affect the activities of other medicines e.g. the gastrointestinal effects of codeine may delay absorption as with *mexiletine* or may be counteractive as with *cisapride, metoclopramide or domperidone*.
- The effects of *atropine* and *tricyclic antidepressants* may be enhanced by *promethazine hydrochloride*.
- Warning symptoms of damage caused by *ototoxic medicines* such as *aminoglycoside antibiotics* may be masked.
- The sedative effect of central nervous system depressants including *alcohol*, *barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives* and *antipsychotics* may be enhanced.
- *Pseudoephedrine hydrochloride* should be avoided or used with caution in patients undergoing *anaesthesia* with *halogenated anaesthetics* as they may induce ventricular fibrillation.
- An increased risk of dysrhythmias may occur if given to patients receiving *cardiac glycosides*, ~~quinidine or~~ tricyclic antidepressants.
- Reversal of the action of *antihypertensive agents* may occur and therefore special care is advisable in patients receiving antihypertensive therapy. Interaction with *alpha- and beta- blocking medicines* may be complex.
- *Amphetamine-like psychostimulants*: risk of hypertension.
- *Oxytocin* – risk of hypertension.
- Enhances effects of *anticholinergic medicines*.

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- *Hepatotoxic medicines* – increased risk of hepatoxicity.
- *Enzyme inducing medicine*s - increased risk of hepatoxicity.
- *Metoclopramide* – absorption of COLCAPS CHILDRENS SYRUP may be accelerated.
- *Cholestyramine* – absorption of COLCAPS CHILDRENS SYRUP is reduced if given within one hour of cholestyramine.
- Excretion may be affected and plasma concentrations altered when given with *probenecid*.

Interactions with laboratory tests

- *Promethazine hydrochloride* should be discontinued at least 72 hours before the start of *skin tests* as it may inhibit the cutaneous histamine response thus producing false-negative results.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established. Do not use in pregnancy. COLCAPS CHILDREN'S SYRUP is contraindicated in breastfeeding mothers. No fertility data available.

4.7 Effects on ability to drive and use machines

COLCAPS CHILDRENS SYRUP may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other medicines which depress the central nervous system. Patients should be warned against activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

The undesirable effects listed are based on the MedDRA system organ classes (SOC)

classification system. The frequency groupings listed conform to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000) and unknown (cannot be estimated from the available data)

Paracetamol

System Organ Class	***Frequency***	***Undesirable effect***
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia and agranulocytosis.
	Unknown	Leucopenia, pancytopenia, neutropenia and anaemia.
Immune system disorders	Less frequent	Allergic reactions.
Gastrointestinal disorders	Unknown	Pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis
Renal and urinary disorders	Less frequent	Renal colic, renal failure and sterile pyuria
Skin and subcutaneous tissue disorders	Less frequent	Skin rash (usually erythematous or urticarial) but sometimes more serious and accompanied by drug fever and mucosal lesions. Dermatitis.

Codeine phosphate

System Organ Class	***Frequency***	***Undesirable effect***
Immune system disorders	Less frequent	Urticaria
Psychiatric disorders	Less frequent	Restlessness and confusion.
	Unknown	Changes of mood, hallucinations.
Nervous system disorders	Frequent	Drowsiness
	Unknown	Headache, dizziness.

Eye disorders	Less frequent	Miosis
	Unknown	Raised intracranial pressure.
Ear and labyrinth disorders	Unknown	Vertigo
Cardiac disorders	Less frequent	Bradycardia and palpitations.
	Unknown	Tachycardia.
Vascular disorders	Less frequent	Orthostatic hypotension.
	Unknown	Hypothermia.
Gastrointestinal disorders	Frequent	Constipation.
	Less frequent	Nausea, vomiting and dry mouth.
Hepatobiliary disorders	Less frequent	Billiary spasm.
Skin and subcutaneous tissue disorders	Less frequent	Sweating, facial flushing and pruritus.
Renal and urinary disorders	Less frequent	Micturition may be difficult, ureteric spasm.
General disorders and administration site conditions	Unknown	Hypothermia

Promethazine hydrochloride

System Organ Class	***Frequency***	***Undesirable effect***
Blood and lymphatic system disorders	Less frequent	Blood dyscrasias and haemolytic anaemia.
	Unknown	Agranulocytosis.
Immune system disorders	Unknown	Allergy and anaphylaxis.
Metabolism and nutrition disorders	Less frequent	Anorexia.
Psychiatric disorders	Unknown	Depression, elation, irritability, nightmares, insomnia and Nervousness, Inability to concentrate
Nervous system disorders	Unknown	Incoordination, tremors, muscular weakness, sedation, tinnitus,

		headache, convulsions, tingling and cerebral stimulation (in infants and children).
Cardiac disorders	Less frequent	Tachycardia.
Vascular disorders	Less frequent	Hypotension and dizziness.
Respiratory, thoracic & mediastinal disorders	Frequent	Tightness of chest.
Gastrointestinal disorders	Less frequent	Dryness of the mouth.
	Unknown	Vomiting, nausea, diarrhoea, constipation, epigastric pain and gastrointestinal disturbances.
Musculoskeletal and connective tissue disorders	Unknown	Muscle twitching, heaviness and weakness of hands.
Renal and urinary disorders	Less frequent	Difficulty in micturition.
General disorders and administration site conditions	Unknown	lassitude.

Pseudoephedrine hydrochloride

System Organ Class	***Frequency***	***Undesirable effect***
Metabolism and nutrition disorders	Unknown	Reduced appetite, altered metabolism and disturbances of glucose metabolism.
Psychiatric disorders	Frequent	Restlessness and insomnia.
	Unknown	Fear, anxiety, confusion, irritability and psychotic state.
Nervous system disorders	Less frequent	Tremor
Cardiac disorders	Less frequent	Palpitations, ~~dizziness, fainting~~ and tachycardia, reflex bradycardia, cardiac

		dysrhythmias, cardiac arrest and dyspnoea.
	Unknown	Anginal pain, cardiac oedema ~~and pulmonary oedema.~~
Vascular disorders	Unknown	Vasoconstriction with resultant hypertension, cerebral haemorrhage, hypotension with dizziness and flushing.
Respiratory, thoracic and mediastinal disorders	Unknown	Pulmonary oedema
Gastrointestinal disorders	Less frequent	Nausea and vomiting.
	Unknown	Hypersalivation
Skin and subcutaneous tissue disorders	Less frequent	Sweating.
Renal and urinary disorders	Less frequent	Difficulty in micturition and urinary retention.
General disorders and administration site conditions	Less frequent	Weakness, fainting

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity.

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 arrhythmias have been reported.

Treatment:

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 be given a single dose of 50 g activated charcoal.

Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose 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 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 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.

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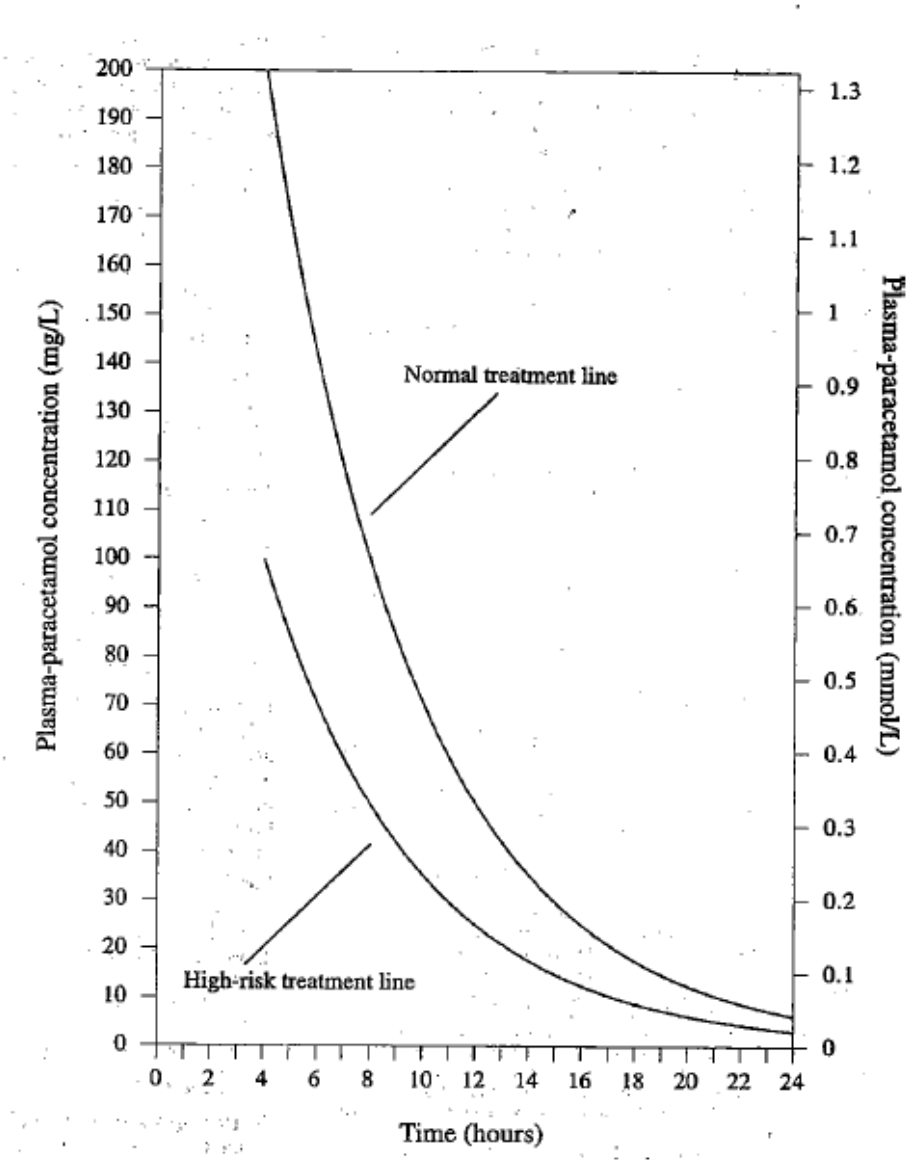

Reference: Martindale 35th Edition

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/ kg IV over 16 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”.

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Prothrombin index correlates best with survival. Monitor all patients with significant ingestions for at least ninety-six hours.

Codeine phosphate:

Symptoms: Following large doses of codeine, excitement and convulsions may occur.

Treatment: Treatment is symptomatic and supportive.

Promethazine hydrochloride:

Symptoms: Overdosage may be fatal especially in infants and children. It is associated with antimuscarinic, extrapyramidal, gastrointestinal and central nervous system (CNS) effects. In infants and children central nervous system (CNS) stimulation predominates over central nervous system (CNS) depression, causing ataxia, excitement, tremors, psychoses, hallucinations, and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, central nervous system (CNS) depression is more common with drowsiness, coma and convulsions, progressing to respiratory failure or possibly cardiovascular collapse.

Treatment: Treatment is symptomatic and supportive.

Pseudoephedrine hydrochloride:

Symptoms: Overdosage with the pseudoephedrine component will result in the excessive stimulation of the central nervous system causing an increase in the severity of the central nervous system (CNS) side effects mentioned.

Treatment: Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

A 5.8 Preparations for common cold, including nasal decongestant and antihistaminic.

WHO ATCC Code: R05 COUGH AND COLD PREPARATIONS

5.1 Pharmacodynamics properties

COLCAPS CHILDREN'S SYRUP has an analgesic, antipyretic, antihistaminic and antitussive properties.

Codeine is an opioid and metabolised to morphine, which in turn exerts an analgesic effect.

Paracetamol has analgesic and antipyretic effects.

Promethazine has antihistaminic and anticholinergic properties.

Pseudoephedrine hydrochloride has decongestant properties.

5.2 Pharmacokinetic properties

The pharmacokinetics of codeine phosphate and promethazine hydrochloride have not yet been studied in children.

Pseudoephedrine:

Pseudoephedrine is readily absorbed from the gastrointestinal tract. It is excreted unchanged in the urine with small amounts of its hepatic metabolite.

Paracetamol:

Paracetamol is well absorbed following oral administration. Peak plasma concentrations occur within 30 to 60 minutes and the half-life in plasma is about 2 hours after therapeutic doses. Paracetamol is distributed relatively uniformly throughout all body fluids. Some 90% to 100% of the drug may be recovered in the first day at therapeutic dosing, primarily after hepatic conjugation. Paracetamol half-life elimination varies from 1-3 hours. It is metabolised mainly in the liver and excreted in the urine as the glucuronide and sulfate conjugates, and less than 5 % is excreted as unchanged paracetamol.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Alcohol
- Ascorbic Acid
- Blackcurrant Flavour
- Citric Acid
- Liquid Glucose
- Methyl Hydroxybenzoate
- Orange Colour
- Orange Sweet Flavour
- Propylene Glycol
- Propyl Hydroxybenzoate
- Purified Water
- Saccharin Sodium
- Sodium Cyclamate
- Sodium Hydroxide Pellets
- Sucrose

6.2 Incompatibilities

No information available.

6.3 Shelf life

24 months.

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6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep in original packaging until required for use.

6.5 Nature and contents of container

100 ml amber glass bottle with a white screw-on closure and an EXPE liner.

6.6 Special precautions for disposal

Not applicable.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, 1685

Private Bag X69

Bryanston, 2021

8. REGISTRATION NUMBER

D/5.8/0054

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 20 November 1972

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10. DATE OF REVISION OF THE TEXT

10 June 2022

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