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REPUBLIC OF FRANCE

Saint Denis, September 15, 2016

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SANOFI-AVENTIS FRANCE
82 AVENUE RASPAIL
94250 GENTILLY
FRANCE

[stamp]
RECEIVED on
September 19, 2016

Dear Sir or Madam,

In your letter dated June 23, 2016, and received on June 27, 2016, in compliance with the provisions of Commission Regulation (EC) No. 1234/2008 of November 24, 2008, and the guidelines for its application, you submitted an application for a type IA variation to the Marketing Authorization for the proprietary medicinal product:

Rhinathiol Promethazine syrup

with the following description: B.III.1.a.2: Submission of an updated Ph. Eur. Certificate of Suitability concerning the active substance carbocisteine*:* R1-CEP 1997-037-REV03.

I would like to inform you that, after review, your application has been approved.

An appeal against this decision can be lodged before the competent administrative court within two months from the date of receipt.

I would also like to inform you that your application(s) for (a) variation(s) mentioned in the enclosed list has/have been approved.

Lastly, this decision is without prejudice to any subsequent measures that may be taken by the Agency in the interests of public health.

Please find enclosed the decision amending the Marketing Authorization for your proprietary medicinal product.

(French formal ending to correspondence)

Director of the Flow Management and Reference Systems Division

(Original French document signed)

Wenceslas Bubenicek

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under Tracking No. SA-CHC-RTS11580 on November 8, 2016

Reason for change		Type (IA/IB/II)	Date of submission to the ANSM	Decision
Code*	**Description**			
0	Type II variation concerning update of section 4.8. "Undesirable effects" in Annex I to the MA	II	Sep. 3, 2012	*Express approval*
0	Type II.C.1.4 variation: "change to the Summary of Product Characteristics and Package Leaflet following new pharmacovigilance data, in accordance with the Global Labeling Update (GLU v.04) for carbocisteine".	II	Feb.12, 2015	*Express approval*
0	Type II.C.1.4 variation: "following new Pharmacovigilance data in accordance with the Global Labeling Update (GLU v.05) for carbocisteine"	II	Oct. 15, 2015	*Express approval*

** see guidelines for Commission Regulation (EC) No. 1234/2008 or the French decree of March 7, 2005 (for applications prior to August 4, 2013)*

References:

NL	CIS
VNL5525	6 931 788 9

Decision

amending the Marketing Authorization for the proprietary medicinal product:

Rhinathiol Promethazine syrup

THE DIRECTOR GENERAL OF THE FRENCH NATIONAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS SAFETY

In view of Commission Regulation (EC) no. 1234/2008 of November 24, 2008 concerning the examination of variations to the terms of Marketing Authorizations for medicinal products for human use and veterinary medicinal products as well as the guidelines relating to its implementation;

In view of the French Public Health Code, Part V, and particularly Articles L.5121-8, L.5121-20, R.5121-21 *et seq.*;

In view of the Marketing Authorization granted on: March 27, 1973;

In view of the application for a change to the Marketing Authorization submitted by:

sanofi-aventis France

on June 23, 2016;

together with the previous applications for changes to which it specifically refers, indicated as having been approved in the notification letter accompanying this decision.

Has decided

Article 1

The Marketing Authorization for the proprietary medicinal product **Rhinathiol Promethazine syrup** held by **sanofi-aventis France** is amended.

Article 2

The information appended to this Decision supersedes the corresponding information in the Annexes to the current Marketing Authorization.

Article 3

The concerned party has been notified of this Decision.

September 15, 2016

Director of the Flow Management and Reference Systems Division

(Original French document signed)

Wenceslas Bubenicek

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rhinathiol Promethazine syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Carbocisteine ..... 2.0000 g

Promethazine hydrochloride ..... 0.0500 g

for 100 ml of syrup.

One 5 ml measuring spoon contains 100 mg of carbocisteine and 2.5 mg of promethazine hydrochloride.
One 15 ml tablespoon contains 300 mg of carbocisteine and 7.5 mg of promethazine hydrochloride.

Excipients: sodium, alcohol, sucrose, methyl parahydroxybenzoate (E218). Alcohol content of the syrup by volume: 3.09% (V/V).
One 5 ml measuring spoon contains 3 g of sucrose and 122 mg of anhydrous ethanol.
One 15 ml tablespoon contains 9 g of sucrose and 366 mg of anhydrous ethanol. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of irritating, non-productive cough, predominantly occurring at night.
Note: combination of a cough suppressant and an expectorant is not justified.

4.2. Posology and method of administration

Oral use.

FOR ADULTS AND CHILDREN OVER 2 YEARS OF AGE ONLY.

Symptomatic treatment should be short-term (a few days) and should only be taken when coughing occurs.

Adults

3 or 4 tablespoons (15 ml) per day.

Children

the measuring spoon provided with this syrup must be used:

- aged 24 to 30 months: three or four 5 ml measuring spoons per day,
- aged 30 months to 12 years: four to six 5 ml measuring spoons per day,
- aged 12 to 15 years: six to nine 5 ml measuring spoons per day.

This medicinal product should preferably be taken in the evening due to the marked sedative effect of promethazine.

4.3. Contraindications

This medicinal product is **contraindicated** in the following situations:

- Hypersensitivity to any of the ingredients, particularly methyl parahydroxybenzoate and other parahydroxybenzoate salts.
- Infants under two years of age (see section 4.4).
- Due to the fact that the medicinal product contains promethazine hydrochloride:

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- o Hypersensitivity to antihistamines.
- o History of agranulocytosis.
- o Risk of urinary retention related to urethro-prostatic disorders.
- o Risk of angle-closure glaucoma.
- o In combination with cabergoline and quinagolide (see section 4.5).

4.4. Special warnings and precautions for use

Special warnings

Productive cough, which is a fundamental bronchopulmonary defense mechanism, should not be suppressed.

It is irrational to combine an expectorant or mucolytic agent with this cough suppressant.

Before prescribing a cough suppressant, the underlying causes of the cough, which require specific treatment, should be investigated.

If the cough does not respond to a cough suppressant administered at the usual dose, the dose must not be increased, but the clinical situation should be reassessed instead.

Mucolytic agents may induce severe bronchial congestion in infants. Infant bronchial mucus drainage capacities are limited due to the physiological characteristics of their bronchial tree. Mucolytics should therefore not be used in infants (see sections 4.3 and 4.8).

Since phenothiazines are considered to be a potential risk factor for sudden infant death syndrome, promethazine should not be used in infants aged under 2 years due to the risk of fatal respiratory depression.

Treatment should be re-evaluated if the symptoms or disease persist or worsen.

NOTE: THIS MEDICINAL PRODUCT CONTAINS ALCOHOL
The alcohol content of the syrup is 3.09%, i.e.:
122 mg of alcohol per measuring spoon (5 ml),
366 mg of alcohol per tablespoon (15 ml).

This medicinal product contains 3.09% V/V ethanol (alcohol), i.e. up to 366 mg per tablespoon of syrup, or 1.46 g of ethanol per maximum daily dose, which is equivalent to not more than 37 ml of beer or 15 ml of wine per day. Use of this medicinal product is dangerous in alcoholics. In pregnant or breast-feeding women, children and high-risk populations such as patients with liver failure or epilepsy, the alcohol content must be taken into account.

Precautions for use

Related to the presence of carbocisteine

Caution is recommended in the elderly, in patients with a history of gastroduodenal ulcers, and in those taking concomitant medications which may cause gastrointestinal bleeding.

If gastrointestinal bleeding occurs, patients should discontinue medication.

Related to the presence of promethazine

Monitoring (clinical and ECG where appropriate) should be increased in patients with epilepsy due to the possible lowering of the seizure threshold.

Promethazine hydrochloride should be used with caution:

- In elderly subjects with:
  - o greater sensitivity to postural hypotension, dizziness and sedation,
  - o chronic constipation (risk of paralytic ileus),
  - o possible prostatic hypertrophy.
- In patients with certain cardiovascular diseases, due to the tachycardia-inducing and hypotensive effects of phenothiazines.
- In patients with severe liver and/or kidney failure (due to the risk of accumulation).

When used in children, bronchial asthma or gastroesophageal reflux should be ruled out before using promethazine as a cough suppressant.

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Intake of alcoholic beverages or medicinal products containing alcohol (see section 4.5) is highly inadvisable during treatment.

Given the photosensitizing effect of phenothiazines, exposure to sun should preferably be avoided during treatment.

H1-antihistamines may cause sedation and should be used with caution. Combination with other sedative medicinal products should be discouraged (see section 4.5).

Related to the excipients

This medicinal product contains sucrose. It is therefore not recommended in patients with fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency.

This medicinal product contains 3 g of sucrose per measuring spoon and 9 g per tablespoon; this should be taken into account in patients on a low-sugar diet or with diabetes mellitus.

This medicinal product contains sodium. This medicinal product contains 13 mg of sodium per 5 ml of syrup. This should be taken into consideration in patients on a strict low-sodium diet.

This medicinal product contains methyl parahydroxybenzoate (E218) and may cause allergic reactions (possibly delayed).

4.5. Interaction with other medicinal products and other forms of interaction

The interactions mentioned are related to the promethazine content.

Seizure threshold-lowering drugs

Use of this drug in combination with seizure-inducing agents or seizure-threshold lowering drugs should be carefully considered due to the high risk for the patient. These drugs include most antidepressants (imipramine agents, selective serotonin reuptake inhibitors), neuroleptics (phenothiazines and butyrophenones), mefloquine, chloroquine, bupropion and tramadol.

Atropine-like drugs

It should be taken into account that atropine-like substances can have additive adverse effects and more easily lead to urinary retention, acute attacks of glaucoma, constipation, dry mouth, etc.
The various atropine-like drugs include imipramine antidepressants, most atropine-like H1-antihistamines, anticholinergic antiparkinsonians, atropine-like antispasmodics, disopyramide, phenothiazine neuroleptics and clozapine.

Sedative drugs

It should be taken into account that many drugs or substances can have additive depressant effects on the central nervous system and contribute to a decrease in alertness. These drugs include morphine derivatives (analgesics, antitussives and replacement therapies), neuroleptics, barbiturates, benzodiazepines, non-benzodiazepine anxiolytics (such as meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1-antihistamines, centrally-acting antihypertensives, baclofen and thalidomide.

Hypnotic agents

Currently prescribed hypnotic agents are either benzodiazepines and related products (zolpidem, zopiclone), or H1-antihistamines. In addition to increased sedation when prescribed with other CNS depressants, or in the event of alcohol intake, the possible increase in the respiratory depressant effect when co-administered with morphine-like substances, other benzodiazepines, or phenobarbital should also be taken into account for benzodiazepines, especially in the elderly.

DRUGS INDUCING POSTURAL HYPOTENSION

In addition to antihypertensive agents, numerous drugs may cause postural hypotension. These include nitrate derivatives, phosphodiesterase type-5 inhibitors, alphablocking agents for urological purposes, imipramine antidepressants and phenothiazine neuroleptics, dopamine agonists and levodopa.

Concomitant use could therefore increase the frequency and severity of this adverse effect. Refer to the interactions specific to each class, with the corresponding obligations.

Contraindicated combinations (see section 4.3):

+ Non-antiparkinsonian dopamine agonists (cabergoline, quinagolide): Mutual antagonism between dopamine agonists and neuroleptics.

Inadvisable combinations (see section 4.4)

+ ALCOHOL intake (BEVERAGE OR EXCIPIENT)
Potentiation of the sedative effects induced by these substances.
Impaired alertness may make driving or using machines dangerous.
The consumption of alcoholic beverages or alcohol-containing medicinal products should be avoided.

Combinations requiring precautions for use

+ Topical agents for gastrointestinal use, antacids and charcoal: Decreased gastrointestinal absorption of phenothiazine neuroleptics.
Allow an interval (2 hours, if possible) between administration of topical gastrointestinal agents or antacids and phenothiazine neuroleptics.

+ Lithium
Risk of occurrence of neuropsychiatric signs suggestive of neuroleptic malignant syndrome or lithium poisoning.
Regular clinical and laboratory monitoring required, especially at the start of co-administration.

Combinations to be taken into consideration

+ Antihypertensive drugs:
Increased risk of hypotension, particularly postural hypotension.

+ Beta-blockers (except esmolol and sotalol):
Vasodilator effect and risk of hypotension, particularly postural (additive effect).

+ Beta-blockers in heart failure (bisoprolol, carvedilol, metoprolol, nebivolol):
Vasodilator effect and risk of hypotension, particularly postural (additive effect).

+ Nitrate derivatives and related substances:
Increased risk of hypotension, particularly hypostatic[1].

+ Other hypnotic agents:
Potentiation of depressant effect on the central nervous system.

+ Orlistat:
Risk of treatment failure if administered concomitantly with orlistat.

- **Dapoxetine:**

Risk of increased adverse effects, particularly dizziness or syncope.

+ Other drugs lowering the seizure threshold:
Increased risk of seizure.

+ Other sedative drugs:

Potentiation of depressant effect on the central nervous system.

Impaired alertness may make driving or using machines dangerous.

+ Other atropine-like drugs

Possibility of additive effects caused by atropine-like substances, such as urinary retention, constipation and dry mouth.

[1] Translator's note: Should probably read "postural".

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4.6. Fertility, pregnancy and lactation

Pregnancy

Malformations (1st trimester)

Animal studies:

- do not indicate any teratogenic effect of carbocisteine,
- have not established any reliable teratogenicity data for promethazine.

In a clinical context:

- no data are available for carbocisteine,
- the use of promethazine during a limited number of pregnancies does not appear to have shown any particular teratogenic or fetotoxic effects to date.

However, additional studies are necessary to evaluate the consequences of exposure during pregnancy.

Fetotoxicity (2nd and 3rd trimesters)
In neonates whose mothers received long-term treatment with strong doses of an anticholinergic antihistamine such as promethazine, there have been rare reports of gastrointestinal disorders related to atropine-like properties of phenothiazines (abdominal distention, meconium ileus, delayed meconium excretion, difficulties instituting feeding, tachycardia, neurological disorders, etc.)

In view of these data, the use of this medicinal product should be avoided as a precautionary measure during the first trimester of pregnancy. It should only be prescribed if absolutely necessary thereafter and prescription should be limited to occasional use in the third trimester.

The use of this medicinal product at the end of pregnancy appears to warrant monitoring of the neonate's neurological and gastrointestinal functions over a certain period.

Breast-feeding

Given that antihistamines are excreted in breast milk, although in small amounts, and given that promethazine has marked sedative properties, use of this medicinal product should be avoided by breast-feeding women.

4.7. Effects on ability to drive and use machines

Patients should be warned about the risk of drowsiness especially at the start of treatment and advised not to drive or operate machinery.

Drinking alcohol or taking medicines that contain alcohol enhances these effects.

4.8. Undesirable effects

Related to the carbocisteine content:

- Risk of bronchial congestion, especially in infants and certain patients unable to expectorate effectively (see sections 4.3 and 4.4).
- Allergic skin reactions such as pruritus, erythematous eruption, urticaria and angioedema.
- Some cases of fixed drug eruption have been reported.
- Gastrointestinal disorders (gastric pain, nausea, vomiting, and diarrhea). If these occur, the dose should be reduced.
- Gastrointestinal bleeding. Treatment should be discontinued.
- Isolated cases of bullous dermatoses, such as Stevens-Johnson syndrome and erythema multiforme.

Related to the promethazine content:

The pharmacological properties of this compound can cause adverse reactions of varying severity related or unrelated to the dose (see section 5.1).

Autonomic nervous system disorders

- sedation or drowsiness, more pronounced at the start of treatment, anticholinergic effects such as dryness of the mucous membranes, constipation, accommodation problems, mydriasis, palpitations, risk of urinary retention,
- postural hypotension,
- balance disorders, dizziness, memory or concentration problems,

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- loss of motor coordination, tremor (more common among the elderly),
- mental confusion, hallucinations,
- more rarely, excitation-type effects, agitation, nervousness, insomnia.

Sensitivity reactions
- erythema, eczema, pruritus, purpura, urticaria and possibly giant urticaria,
- asthma attack,
- edema, more rarely angioedema,
- anaphylactic shock,
- photosensitization.

Hematological effects
- leukopenia, neutropenia and, exceptionally, agranulocytosis,
- thrombocytopenia,
- hemolytic anemia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system, i.e. "*Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)"* under "*Réseau des Centres de Pharmacovigilance" (*Network of Pharmacovigilance Centers) - website: www.ansm.sante.fr.

4.9. Overdose

Signs of promethazine overdose

Seizures (especially in children), consciousness disorders, coma. Symptomatic treatment is to be instituted in a specialized environment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ANTIHISTAMINE FOR SYSTEMIC USE
(R: Respiratory system).

Promethazine
H1-antihistamine, phenothiazine with aliphatic side chain, characterized by:
- a marked sedative effect at the usual doses, by antagonizing central H1 receptors and central adrenergic blocking,
- an anticholinergic effect, responsible for peripheral adverse effects,
- a peripheral adrenergic blocking effect, with possible hemodynamic consequences (risk of postural hypotension).

Antihistamines share the property of blocking the effects of histamine, particularly on the skin, in the bronchi, intestine and blood vessels, by more or less reversible competitive antagonism.

In most cases, they have a cough suppressant effect which in itself is moderate, but which potentiates the effects of centrally-acting morphine cough suppressants, as well as those of other bronchodilators such as sympathomimetic amines with which they are often co-administered.

5.2. Pharmacokinetic properties

Orally administered **carbocisteine** is rapidly absorbed; peak plasma concentrations are reached in two hours.
Bioavailability is low (less than 10% of the administered dose), probably as a result of intraluminal metabolism and a marked liver first-pass effect.
Elimination half-life is approximately 2 hours.
Carbocisteine and its metabolites are eliminated primarily in the urine.

The bioavailability of **promethazine** is between 13 and 40%.
The time to reach plasma concentrations is 1.5 to 3 hours.
The volume of distribution is high due to the liposolubility of the compound, approximately 15 l/kg.
The drug is 75-80% plasma protein bound.
The half-life is between 10 and 15 hours.

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Metabolism consists of sulfoxidation followed by demethylation.
Renal clearance represents less than 1% of total clearance and approximately 1% of administered promethazine is detected unchanged in the urine.
The metabolites found in the urine, notably in sulfoxide form, represent approximately 20% of the dose.

Pathophysiological variation: risk of accumulation of antihistamines in patients with kidney or liver failure.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose, methyl parahydroxybenzoate (E218), powdered caramel coloring agent (E150), cocoa flavoring*, vanillin, ethanol, sodium hydroxide, purified water.
*qualitative composition of the cocoa flavoring: vanilla tincture, cocoa alcohol extract, with added vanillin, acetic, butyric, caproic, isobutyric, valeric acid esters, ethyl, butyl, amyl, hexyl alcohol esters, and solvent: ethyl alcohol, propylene glycol.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

125 or 200 ml in a type III amber glass bottle crimp-sealed with an aluminum cap, with a 5 ml polystyrene measuring spoon.

125 or 200 ml in a type III amber glass bottle crimp-sealed with a polypropylene child-proof cap, with a 5 ml polystyrene measuring spoon.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

sanofi-aventis France
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORIZATION NUMBER(S)

- 34009 309 090 8 9: 125 ml in (amber glass) bottles + (polystyrene) measuring spoon.
- 34009 222 854 6 7: 125 ml in (amber glass) bottles with (polypropylene) child-proof cap + (polystyrene) measuring spoon.
- 34009 363 688 5 9: 200 ml in (amber glass) bottles + (polystyrene) measuring spoon.
- 34009 222 855 2 8: 200 ml in (amber glass) bottles with (polypropylene) child-proof cap + (polystyrene) measuring spoon.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

[to be filled in by the MA holder]

10. DATE OF REVISION OF THE TEXT

[to be filled in by the MA holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.

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ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

A.1 Name and address of the manufacturer(s) of the biological active substance(s)

Not applicable.

A.2 Name and address of the manufacturers responsible for batch release

Unither Liquid Manufacturing
1-3 allée de la Neste
31770 Colomiers
France

or

Sanofi-Winthrop Industrie
Route de Saint-Lô
Z.I. de la Guérie
50200 Coutances
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product not subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

Not applicable.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORIZATION MEASURES FOR THE MARKETING AUTHORIZATION UNDER EXCEPTIONAL CIRCUMSTANCES

Not applicable.

F. QUALITATIVE AND QUANTITATIVE COMPOSITION IN EXCIPIENTS

Sucrose ..... 60.0000 g

Methyl parahydroxybenzoate (E218) ..... 0.1500 g

Powdered caramel coloring agent (E151) ..... 0.0126 g

Cocoa flavoring* .....0.5000 ml

Vanillin ..... 0.0250 g

Alcohol ..... 2.3000 g

Sodium hydroxide .....q.s. pH 6.10-6.30

Purified water ..... q.s. 100.0000 ml

For 100.0000 ml of syrup.

*Qualitative composition of the cocoa flavoring: vanilla tincture, cocoa alcohol extract, with added vanillin, acetic, butyric, caproic, isobutyric, valeric acid esters, ethyl, butyl, amyl, hexyl alcohol esters, and solvent: ethyl alcohol, propylene glycol. Alcohol content of the syrup by volume: 3.09% (V/V).
One 5 ml measuring spoon contains 3 g of sucrose and 122 mg of anhydrous ethanol.
One 15 ml tablespoon contains 9 g of sucrose and 366 mg of anhydrous ethanol.

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ANNEX IIIA

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

NATURE/TYPE OUTER PACKAGING OR IMMEDIATE PACKAGING

Outer packaging and bottle.

1. NAME OF THE MEDICINAL PRODUCT

Rhinathiol Promethazine syrup

Carbocisteine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Carbocisteine ..... 2.0000 g

Promethazine hydrochloride ..... 0.0500 g

For 100 ml of syrup.

One 5 ml measuring spoon contains 100 mg of carbocisteine and 2.5 mg of promethazine hydrochloride.

One 15 ml tablespoon contains 300 mg of carbocisteine and 7.5 mg of promethazine hydrochloride.

3. LIST OF EXCIPIENTS

Excipients with known effect: sodium, ethanol (alcohol), sucrose, methyl parahydroxybenzoate (E218).

4. PHARMACEUTICAL FORM AND CONTENTS

Syrup.

125 or 200 ml bottle with a 5 ml measuring spoon.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

NOTE: THIS MEDICINAL PRODUCT CONTAINS ALCOHOL
The alcohol content of the syrup is 3.09%, i.e.:
The alcohol content of the syrup is 3.09%, i.e.:
366 mg of alcohol per tablespoon (15 ml).

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8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable.

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder

sanofi-aventis France
82 Avenue Raspail
94250 Gentilly
France

Operator

sanofi-aventis France
82 Avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORIZATION NUMBER(S)

Marketing Authorization No.:

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.

15. INSTRUCTIONS ON USE

This medicinal product is recommended for the relief of dry and irritating coughs in adults and children aged over 2 years, especially when occurring in the evening or at night.

16. INFORMATION IN BRAILLE

As per current legislation.

PICTOGRAM TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

The pictogram must comply with the French decree dated August 8, 2008 in application of Article R.5121-139 of the French Public Health Code related to use of a pictogram on the outer packaging of certain medicines and products.

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MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

NATURE/TYPE BLISTERS/STRIPS

Not applicable.

1. NAME OF THE MEDICINAL PRODUCT

Not applicable.

2. NAME OF THE MARKETING AUTHORIZATION HOLDER

Not applicable.

3. EXPIRY DATE

Not applicable.

4. BATCH NUMBER

Not applicable.

5. OTHER

Not applicable.

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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

NATURE/TYPE SMALL IMMEDIATE PACKAGING UNITS

Not applicable.

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Not applicable.

2. METHOD OF ADMINISTRATION

Not applicable.

3. EXPIRY DATE

Not applicable.

4. BATCH NUMBER

Not applicable.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Not applicable.

6. OTHER

Not applicable.

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ANNEX IIIB

PACKAGE LEAFLET: INFORMATION FOR THE USER

Name of the medicinal product

Rhinathiol Promethazine syrup

Carbocisteine

Boxed text

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You must talk to a doctor if you do not feel better or if you feel worse.

Keep out of the reach of children.

What is in this leaflet

1. WHAT Rhinathiol Promethazine syrup IS AND WHAT IT IS USED FOR

Pharmacotherapeutic group: Rhinathiol Promethazine is a cough suppressant belonging to a group of medicines called antihistamines.

It blocks the effects of histamine, especially on the bronchi.

This medicine also contains carbocisteine.

This medicine is used to relieve dry and irritating cough, especially when occurring in the evening or at night.

Rhinathiol Promethazine is for adults and children aged over 2 years only.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE Rhinathiol Promethazine syrup

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Do not take Rhinathiol Promethazine syrup:

- if you are allergic to any of the active substances (promethazine or carbocisteine) or any of the other ingredients of Rhinathiol Promethazine. See section 6 for the full list of ingredients.
- if you are allergic to a medicine belonging to the same group as Rhinathiol Promethazine (antihistamines) used to treat allergies.
- if you have previously experienced a major drop in the number of certain white blood cells known as granulocytes (agranulocytosis).
- if you are at risk of narrow-angle glaucoma (increased pressure inside the eye with a possible impact on eyesight).
- if you experience difficulty passing urine (due to prostate or other disorders).

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- if you are taking medicine containing cabergoline or quinagolide (used to reduce excessive prolactin production).
- in children aged under 2 years.

Warnings and precautions

Take special care with Rhinathiol Promethazine

NOTE: THIS MEDICINE CONTAINS ALCOHOL:
The alcohol content of the syrup is 3.09%, i.e.:
- 122 mg of alcohol per measuring spoon (5 ml),
- 366 mg of alcohol per tablespoon (15 ml).

Infants: if your infant has a cough, you should see a doctor.

- This medicine must not be used in infants aged under 2 years because of the risk of serious respiratory disorders related to the promethazine and carbocisteine content of the syrup.
- If cough persists despite using Rhinathiol Promethazine, do not increase the doses. Contact your doctor. Cough is a symptom which can have different causes: respiratory infection, bronchitis, influenza, allergy, asthma, whooping cough, irritation, etc.

Furthermore, tobacco use causes coughing to worsen or persist.

- There are 2 types of cough: dry cough and productive cough. You should not use this medicine to treat a productive cough. Productive cough is a natural defense mechanism which is necessary in order to expel bronchial secretions (mucus).
- If a productive cough develops, with congestion, sputum or fever, ask your doctor for advice.
- Do not attempt to treat a productive cough by using a syrup for productive cough at the same time as this medicine.
- You should avoid exposure to sun and ultraviolet radiation (UVA) during treatment.

Talk to your doctor before taking Rhinathiol Promethazine syrup:

- If you have chronic bronchial or pulmonary disease involving coughing and production of sputum.
- If you have chronic liver disease (severe liver failure) or kidney disease (severe kidney failure). Your doctor should adapt the dose to your condition.
- if you have cardiovascular disease.
- If you have epilepsy.
- If you are aged over 65 years (particularly if you experience chronic constipation, difficulty passing urine due to an enlarged prostate, hypotension, dizziness or drowsiness).
- If your child has asthma or gastroesophageal reflux.
- This medicine may cause drowsiness and should be used with caution.
- If you have a gastroduodenal ulcer (affecting the stomach or intestine).
- During co-administration with medicines liable to cause bleeding in the stomach or intestine.

Treatment should be stopped if bleeding in the stomach or intestine occurs.

During treatment, tell your doctor:

- If you experience fever with or without signs of infection (sore throat, etc.), paleness or sweating.

Other medicines and Rhinathiol Promethazine syrup

This medicine contains an antihistamine, promethazine, and carbocisteine. Other medicines also contain these substances. Do not co-administer these products, so as not to exceed the maximum recommended dose (see section 3 "How to take Rhinathiol Promethazine").

Do not take Rhinathiol Promethazine with medicines containing cabergoline or quinagolide (used to reduce excessive prolactin production).

Avoid taking medicines containing alcohol during treatment.

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Numerous medicines (especially sedative drugs) can reduce alertness. Co-administration with Rhinathiol Promethazine may increase this effect.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Rhinathiol Promethazine syrup with food and drink

You should avoid drinking alcoholic beverages and taking medicines containing alcohol during treatment.

Pregnancy and breast-feeding

Pregnancy

- At the end of pregnancy, taking excessive amounts of this medicine can have harmful effects on the newborn baby.
- If you discover that you are pregnant during treatment, talk to your doctor as soon as possible. Only your doctor will be able to adapt your treatment to your condition.

Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding

As a precautionary measure, breast-feeding is not recommended for newborns.

Ask your doctor or pharmacist for advice before taking any medicine.

Athletes

Not applicable.

Driving and using machines

This medicine may cause drowsiness, especially at the start of treatment. Driving or using machines is not recommended if you experience this effect.

The risk of drowsiness increases if you drink alcoholic beverages or take medicines containing alcohol.

Contents of Rhinathiol Promethazine syrup

- This medicine contains sucrose, consisting of glucose and fructose. It is therefore not recommended for use in patients with fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency (rare hereditary diseases).
- This medicine contains 3 g of sucrose per 5 ml measuring spoon and 9 g per tablespoon. This should be taken into account in patients on a low-sugar diet or with diabetes mellitus.
- This medicine contains 3.09% V/V ethanol (alcohol), i.e., up to 366 mg per tablespoon of syrup, or 1.46 g of ethanol per maximum daily dose (60 ml), which is equivalent to not more than 37 ml of beer or 15 ml of wine per day. Use of this drug is dangerous in alcoholics. In pregnant or breast-feeding women, children and high-risk populations such as patients with liver failure or epilepsy, the alcohol content must be taken into account.
- This medicine contains parahydroxybenzoate and can cause allergic reactions.
- This medicinal product contains 13 mg of sodium per 5 ml of syrup. This should be taken into account if patients are on a controlled sodium diet.

3. HOW TO TAKE Rhinathiol Promethazine syrup

Dosage

This medicine is for adults and children aged over 2 years only.

Always follow the dose recommended in this leaflet. Check with your doctor or pharmacist if you are not sure.

This medicine has been dispensed to you personally, in a specific situation:
- it may be unsuitable in other situations.
- do not pass it on to others.

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Adults:

The usual dose is 3 or 4 tablespoons of syrup per day (one tablespoon is equivalent to 15 ml of syrup).

Children aged 2 to 15 years:

Use the 5 ml measuring spoon provided with this syrup. Wash the measuring spoon after each use.

The daily dose depends on your child's age:

- Children aged 24 to 30 months: three or four 5 ml measuring spoons per day.
- Children aged 30 months to 12 years: four to six 5 ml measuring spoons per day.
- Children aged 12 to 15 years: six to nine 5 ml measuring spoons per day.

Method of administration

This medicine should be taken by mouth.

The measuring spoon provided with the bottle of syrup is to be used for children only.

Duration of treatment

Treatment should be short-term (a few days) and should only be taken when coughing occurs.

If you take more Rhinathiol Promethazine syrup than you should:

Contact your doctor or the emergency services immediately. Rhinathiol Promethazine overdose may cause seizures (especially in children), impaired alertness and coma.

If you forget to take Rhinathiol Promethazine syrup:

Do not take a double dose to make up for a forgotten dose.

If you stop taking Rhinathiol Promethazine syrup:

Not applicable.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

- worsening of bronchial congestion, especially in infants and certain patients unable to cough up sputum effectively.
- stomach pain, nausea, vomiting, diarrhea. If these occur, the dose should be reduced.
- Bleeding in the stomach or intestine. Treatment should be stopped.
- allergic skin reactions such as itching, skin rash, hives and swelling of the face.
- fixed drug eruption (brown marks on the skin).
- Appearance of spots, sometimes with blisters, on the skin that can also affect the mouth (erythema multiforme), appearance of blisters with detachment of the skin that can spread over the whole body and may be life-threatening (Stevens-Johnson syndrome).

Stop the treatment and contact your doctor immediately:

- If you have signs of allergy to the medicine, such as:
  - redness, itching (pruritus), eczema, purple marks on the skin (purpura),
  - hives,
  - edema, sudden swelling of the face and/or neck that can lead to difficulty breathing and be life-threatening (angioedema),
  - asthma attack,
  - sudden malaise with a significant decrease in blood pressure (anaphylactic shock).
- If you have an excessive skin reaction after exposure to sun or UV radiation.
- If you have symptoms possibly caused by a decrease in white blood cell, platelet or red blood cell counts. These symptoms can be recognized by:
  - fever, sometimes with infection (caused by a major drop in white blood cell count),
  - nosebleed or bleeding gums (caused by an abnormal reduction in platelet count).

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The following effects can occur more frequently:

- drowsiness, reduced alertness, particularly at the start of treatment,
- memory or concentration disorders, dizziness (especially in patients aged over 65 years),
- difficulty in coordinating movements, tremor,
- confusion, hallucinations,
- dry mouth, visual disturbances, difficulty passing urine (urinary retention), constipation, heart palpitations, major drop in blood pressure upon standing up, which sometimes causes dizziness and/or malaise (postural hypotension).

More rarely:

- agitation, nervousness, insomnia.

Reporting of side effects

Reporting suspected adverse reactions after authorization 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 national reporting system, i.e. "*Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)"* under "*Réseau des Centres de Pharmacovigilance" (*Network of Pharmacovigilance Centers) - website: www.ansm.sante.fr.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rhinathiol Promethazine syrup

Keep this medicine out of the sight and reach of children.

Do not use Rhinathiol Promethazine after the expiry date which is stated on the bottle. Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATIONS

What Rhinathiol Promethazine syrup contains

The active substance is:

Carbocisteine ..... 2.00 g

Promethazine hydrochloride..... 0.05 g

for 100 ml of syrup.

The other ingredients are: sucrose, methyl parahydroxybenzoate (E218), powdered caramel coloring agent (E150), cocoa flavoring (vanilla tincture, cocoa alcohol extract, with added vanillin, acetic, butyric, caproic, isobutyric, valeric acid esters, ethyl, butyl, amyl, hexyl alcohol esters, and solvent: ethyl alcohol, propylene glycol), vanillin, alcohol, sodium hydroxide, purified water.

1 measuring spoon (5 ml) contains: 100 mg of carbocisteine, 2.5 mg of promethazine hydrochloride, 3 g of sucrose and 122 mg of alcohol.

What Rhinathiol Promethazine syrup looks like and contents of the pack

This medicine is a syrup.
Each pack contains a 125 or 200 ml bottle and a 5 ml measuring spoon.

Marketing Authorization Holder

sanofi-aventis France
82 Avenue Raspail
94250 Gentilly
France

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Operator

sanofi-aventis France
82 Avenue Raspail
94250 Gentilly
France

Manufacturer

Unither Liquid Manufacturing
31770 Colomiers
France

or

Sanofi-Winthrop Industrie
50200 Coutances
France

Names of the medicinal product in the Member States of the European Economic Area

Not applicable.

This leaflet was last revised in:

[to be filled in by the MA holder]

Other

Detailed information about this medicine is available on the ANSM website (France).

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