SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Multi-Action ACTIFED Chesty Coughs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
TRIPROLIDINE HYDROCHLORIDE  1.25 mg
PSEUDOEPHEDRINE HYDROCHLORIDE  30.0 mg
GUAIFENESIN  100.0 mg

3. PHARMACEUTICAL FORM
Oral solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Multi-Action ACTIFED Chesty Coughs is indicated for the symptomatic relief of upper respiratory tract disorders accompanied by productive cough, which are benefited by the combination of a histamine H$_1$-receptor antagonist, a decongestant of the mucous membranes of the upper respiratory tract, especially the nasal mucosa and sinuses, and an expectorant.

4.2 Posology and method of administration

Adults and children aged 12 years and over:
Oral. 10 ml every 4-6 hours up to 4 times a day

Children under 12 years
Multi-Action ACTIFED Chesty Coughs is contraindicated in children under the age of 12 years (see section 4.3)
Multi-Action ACTIFED Chesty Coughs may be diluted 1:1 (1 in 2) or 1:3 (1 in 4) with unpreserved syrup BP. These dilutions have a shelf life of 4 weeks if stored at 25°C.

Use in the Elderly
No specific studies have been carried out in the elderly. Experience has indicated that normal adult dosage is appropriate.

Hepatic Dysfunction
Caution should be exercised when administering Multi-Action ACTIFED Chesty Coughs to patients with severe hepatic impairment.

Renal Dysfunction
Caution should be exercised when administering Multi-Action ACTIFED Chesty Coughs to patients with moderate to severe renal impairment.

Do not exceed the stated dose.

Keep out of the reach and sight of children.

4.3 Contraindications

Multi-Action ACTIFED Chesty Coughs is contraindicated in individuals with known hypersensitivity to the product, any of its components, or acrivastine.

Multi-Action ACTIFED Chesty Coughs is contraindicated in individuals with severe hypertension or severe coronary artery disease.

Multi-Action ACTIFED Chesty Coughs is contraindicated in individuals who are taking, or have taken, monoamine oxidase inhibitors within the preceding two weeks. The concomitant use of pseudoephedrine and this type of product may occasionally cause a rise in blood pressure.

Not to be used in children under the age of 12 years.

4.4 Special warnings and precautions for use

Although pseudoephedrine has virtually no pressor effects in normotensive patients, Multi-Action ACTIFED Chesty Coughs should be used with caution in individuals suffering mild to moderate hypertension.

As with other sympathomimetic agents, Multi-Action ACTIFED Chesty Coughs should be used with caution in individuals with heart disease, hyperthyroidism, diabetes, elevated intra-ocular pressure or prostatic enlargement.
Multi-Action ACTIFED Chesty Coughs should not be used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.

Multi-Action ACTIFED Chesty Coughs may cause drowsiness and impair performance in tests of auditory vigilance. There is individual variation in response to antihistamines.

Caution should be exercised when using the product in the presence of severe hepatic impairment or moderate to severe renal impairment (particularly if accompanied by cardiovascular disease).

Not more than 4 doses should be given in any 24 hours.
Do not exceed the stated dose.
Do not take with any other cough and cold medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Although there are no objective data, users of Multi-Action ACTIFED Chesty Coughs should avoid concomitant use of alcohol or other centrally acting sedatives.

Concomitant use of Multi-Action ACTIFED Chesty Coughs with tricyclic antidepressants, sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) or with monoamine oxidase inhibitors, which interfere with the catabolism of sympathomimetic amines, may occasionally cause a rise in blood pressure.

Because of its pseudoephedrine content, Multi-Action ACTIFED Chesty Coughs may partially reverse the hypotensive action of drugs which interfere with sympathetic activity including bretylium, betanidine, guanethidine, debrisoquine, methyldopa, alpha-and beta-adrenergic blocking agents.

If urine is collected within 24 hours of a dose of Multi-Action ACTIFED Chesty Coughs, a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

4.6 Pregnancy and lactation

Insufficient information is available on the effects of administration of Multi-Action ACTIFED Chesty Coughs during human pregnancy. Like most medicines, it should not be used during pregnancy unless the potential benefit
of treatment to the mother outweighs any possible risk to the developing foetus.

Pseudoephedrine and triprolidine are excreted in breast milk in small amounts but the effect of this on breast-fed infants is not known. It has been estimated that, following the ingestion of a single dose of Multi-Action ACTIFED Tablets/Syrup (2.5 mg triprolidine + 60 mg pseudoephedrine) by a nursing mother, approximately 0.4 to 0.7% of pseudoephedrine and 0.06% to 0.2% triprolidine in the dose will be excreted in the breast milk over 24 hours.

Guaifenesin is excreted in breast milk in small amounts with no effect expected on the infant.

4.7 Effects on ability to drive and use machines

It is recommended that patients are advised not to engage in activities requiring mental alertness, such as driving a car or operating machinery, until they have established their own response to this medicine.

4.8 Undesirable effects

PSEUDOEPHEDRINE - serious adverse effects associated with the use of pseudoephedrine are extremely rare. Symptoms of central nervous system excitation may occur including sleep disturbance and, rarely, hallucinations. Skin rashes with or without irritation and tachycardia have occasionally been reported with pseudoephedrine. Urinary retention has been reported in men receiving pseudoephedrine; prostatic enlargement could have been a predisposing factor.

TRIPROLIDINE - triprolidine may cause drowsiness. Skin rashes, with or without irritation have occasionally been reported. Dryness of the mouth, nose and throat may occur.

GUAIFENESIN - side effects resulting from guaifenesin administration are very rare.

4.9 Overdose

Signs and symptoms - the effects of acute toxicity from Multi-Action ACTIFED Chesty Coughs may include drowsiness, irritability, restlessness, lethargy, dizziness, gastro-intestinal discomfort, nausea, vomiting, difficulty with micturition, dryness of the skin and mucous membranes, ataxia, weakness, hypotonicity, respiratory depression, hyperpyrexia, hyperactivity, convulsions, tremor, tachycardia, palpitations, hypertension.
**Treatment**

Necessary measures should be taken to maintain and support respiration and control convulsions. Gastric lavage may be undertaken if indicated. Catheterisation of the bladder may be necessary. Acid diuresis can accelerate the elimination of pseudoephedrine, although the potential therapeutic gain of this procedure is now in dispute. The value of dialysis in overdose is not known, although four hours of haemodialysis removed approximately 20% of the total body load of pseudoephedrine in a combination product containing 60mg pseudoephedrine and 8mg acrivastine.

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**5. PHARMACOLOGICAL PROPERTIES**

5.1 Pharmacodynamic properties

*Pseudoephedrine*

Pseudoephedrine has direct and indirect sympathomimetic activity and is an effective upper respiratory decongestant. Pseudoephedrine is less potent than ephedrine in producing both tachycardia and elevation of systolic blood pressure and is also less potent in causing stimulation of the central nervous system. Pseudoephedrine produces its decongestant effect within 30 minutes, persisting for at least 4 hours.

*Triprolidine*

Triprolidine is a potent, competitive H₁-receptor antagonist. Being an alkylamine the drug possesses minimal anticholinergic activity. Triprolidine provides symptomatic relief in conditions believed to depend wholly, or partly, upon the triggered release of histamine. After oral administration of a single dose of 2.5 mg triprolidine to adults, the onset of action, as determined by the ability to antagonise histamine-induced wheals and flares in the skin, was within 1 to 2 hours. Peak effects occurred at about 3 hours, and although activity declines thereafter, significant inhibition of histamine-induced wheals and flares still occurred 8 hours after a single dose.

*Guaifenesin*

Guaifenesin is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and reflexly increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centres in the brain which in turn enhance respiratory fluid flow. Guaifenesin produces its expectorant action within 24 hours.
5.2 Pharmacokinetic Properties

ABSORPTION
Pseudoephedrine and triprolidine are well absorbed from the gut following oral administration. After the administration of one Multi-Action ACTIFED Tablet or 10 ml Multi-Action ACTIFED Syrup (each containing 2.5 mg triprolidine and 60 mg pseudoephedrine) to healthy adult volunteers, the following pharmacokinetic values were found;

PSEUDOEPHEDRINE - the $C_{\text{max}}$ of pseudoephedrine was approximately 180 ng/ml for both the tablet and syrup with $t_{\text{max}}$ occurring at approximately 2.0 hours for the tablet and 1.5 hours for the syrup after drug administration.

TRIPROLIDINE - the peak plasma concentration ($C_{\text{max}}$) of triprolidine was approximately 5.5 ng/ml-6.0 ng/ml, occurring at about 2.0 hours ($t_{\text{max}}$) for the tablet and 1.5 hours for the syrup after drug administration.

GUAIIFENESIN - guaifenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information is available on its pharmacokinetics. After the administration of 600 mg guaifenesin to healthy volunteers, the $C_{\text{max}}$ was approximately 1.4 $\mu$g/ml, with $t_{\text{max}}$ occurring approximately 15 minutes after drug administration.

DISTRIBUTION
The apparent volume of distribution of pseudoephedrine ($V_d/F$) was approximately 2.8 l/kg. The apparent volume of distribution of triprolidine was approximately 6.5 l/kg for the tablet formulation and 7.5 l/kg for the syrup. No information is available on the distribution of guaifenesin in humans.

METABOLISM AND ELIMINATION
PSEUDOEPHEDRINE - the $t_{\text{1/2}}$ was approximately 5.5 hours. Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite. Pseudoephedrine and its metabolite are excreted in the urine; 55% to 90% of a dose is excreted unchanged. The apparent total body clearance of pseudoephedrine ($C_1/F$) was approximately 7.5 ml/min/kg. The elimination rate constant ($K_{\text{el}}$) was approximately 0.13 h$^{-1}$. The rate of urinary elimination is accelerated when the urine is acidified. Conversely, as the urine pH increases, the rate of urinary elimination is slowed.

TRIPROLIDINE - the plasma half-life ($t_{\text{1/2}}$) of triprolidine was approximately 3.2 hours. Animal hepatic microsomal enzyme studies have revealed the presence of several triprolidine metabolites with an oxidised product of the toluene methyl group predominating. In man, it has been reported that only about 1% of an administered dose is eliminated as unchanged triprolidine over a 24-hour period. The apparent total body clearance of triprolidine ($C_1/F$) was approximately 30-37 ml/min/kg. The elimination rate constant ($K_{\text{el}}$) was approximately 0.26 h$^{-1}$. 
GUAIFENESIN - guaifenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaifenesin to 3 healthy male volunteers, the $t_{1/2}$ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

PHARMACOKINETICS IN RENAL IMPAIRMENT
Following the administration of a single dose of DUACT CAPSULES (8mg acrivastine + 60 mg pseudoephedrine) to patients with varying degrees of renal impairment, the $C_{max}$ for pseudoephedrine increased approximately 1.5 fold in patients with moderate to severe renal impairment when compared to the $C_{max}$ in healthy volunteers. The $t_{max}$ was not affected by renal impairment. The $t_{1/2}$ increased 3 to 12 fold in patients with mild to severe renal impairment respectively, when compared to the $t_{1/2}$ in healthy volunteers.

There have been no specific studies of Multi-Action ACTIFED Chesty Coughs, triprolidine or guaifenesin in renally impaired patients.

PHARMACOKINETICS IN HEPATIC IMPAIRMENT
There have been no specific studies of Multi-Action ACTIFED Chesty Coughs, triprolidine, pseudoephedrine or guaifenesin in hepatic impairment.

PHARMACOKINETICS IN THE ELDERLY
In elderly volunteers, following the administration of DUACT Capsules (8 mg acrivastine + 60 mg pseudoephedrine), the $t_{1/2}$ for pseudoephedrine was 1.4 fold that seen in healthy volunteers. The apparent Cl/F was 0.8 fold that seen in healthy volunteers, and the Vd/F was essentially unchanged. There have been no specific studies of Multi-Action ACTIFED Chesty Coughs, triprolidine or guaifenesin in the elderly.

5.3 Preclinical safety data
There is insufficient information available to determine whether some of the active ingredients have mutagenic, carcinogenic, teratogenic potential, or the potential to impair fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol solution
Sucrose
Sodium benzoate
Methyl hydroxybenzoate
FD and C yellow No 6 (E 110)
Ethanol (96 per cent)
6.2 Incompatibilities
None Known

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 25°C. Do not refrigerate.
Store in the original container to protect from light.

6.5 Nature and contents of container
100 ml amber glass bottles with a 2 piece or a 3 piece plastic child resistant, tamper evident closure fitted with a polyvinylidene chloride (PVDC) faced wad.
A spoon with a 5ml and a 2.5ml measure is supplied with this product.

6.6 Instructions for use/handling
None applicable

7 MARKETING AUTHORISATION HOLDER

McNeil Products Limited
Foundation Park
Roxborough Way
Maidenhead
Berkshire
8. MARKETING AUTHORISATION NUMBER(S)

PL 15513/0011

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

28 February 1997

10 DATE OF REVISION OF THE TEXT

04/03/2010