SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ANSIMAR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

400 mg tablets
Each tablet contains:
Active ingredient
Doxofylline 400 mg

Ampoules
Each 10 ml ampoule contains:
Active ingredient
Doxofylline 100 mg

Sachets (for pediatric use)
Each sachet contains:
Active ingredient
Doxofylline 200 mg

Syrup
100 ml of syrup contain:
Active ingredient
Doxofylline 2 g

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORMS
400 mg tablets
100 mg/10 ml ampoules
200 mg sachets for pediatric use
2 g/100 ml syrup

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
Bronchial asthma.
Pulmonary disease associated with bronchospasm.

4.2. Posology and method of administration

400 mg tablets – adults: 1 tablet two/three times daily

100 mg ampoules – adults: 2 ampoules by slow intravenous injection to patients in supine position (15-20 minutes), preferably diluted, during the acute phase.
Administration can be repeated at 12 hour intervals, at the physician's discretion.

200 mg sachets - children aged 6-12 years
1-3 sachets per day (12-18 mg/kg) dissolved in plenty of water.

2% syrup: - adults: one 20 ml measures two/three times a day (one 20 ml measure corresponds to 400 mg of doxofylline)

At the recommended posology, the plasma levels of Doxofylline do not generally exceed 20 µg/ml, so it is not essential to check these levels periodically.
If the dosage is increased, the blood levels of the drug must be measured (the therapeutic value is about 10 µg/ml, the value bordering on toxicity is 20 µg/ml).

4.3. Contraindications

ANSIMAR is contraindicated in individuals with known hypersensitivity to the drug or other xanthine derivatives. It is also contraindicated in patients with acute myocardial infarction, hypotension and during lactation.

4.4. Special warnings and precautions for use

Numerous factors may reduce the hepatic clearance of xanthine derivatives with increased plasma levels of the drug. These factors include age, congestive cardiac decompensation, chronic obstructive pulmonary disease, severe liver disease, concomitant infections, the concurrent administration of several drugs such as: erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine and propranolol. In these cases, it may prove necessary to reduce the dosage of the drug.
Phenytoin, other anticonvulsants and cigarette smoking may increase the clearance of xanthine derivatives with a reduction of plasmatic half-life. In these cases, it may prove necessary to increase the dosage of the drug.
In case of factors that may influence the clearance of xanthine derivatives, monitoring of the concentration of the blood levels of the drug is recommended for the control of the therapeutic range.
Caution should be observed in administering the product to patients with cardiac disease, hypertension, in the elderly, in patients with severe hypoxemia, hyperthyroidism, chronic cor pulmonale, congestive heart failure, liver disease, peptic ulcer and in those with renal impairment. In particular, it is to be used with caution in patients with congestive heart failure, since the clearance of the drug is considerably slower in these patients in which high blood levels may persist for long periods even after discontinuation of the treatment.
There is no risk of addiction or any other form of dependence.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

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

ANSIMAR should not be administered with other xanthine preparations. It is recommended to limit consumption of beverages and food containing caffeine .
Caution should be exercised in administering ANSIMAR together with ephedrine or other sympathomimetic drugs.

The concurrent administration of many drugs such as erythromycin, TAO, lincomycin, clindamycin, allopurinol, cimetidine, influenza vaccine and propranolol may reduce the hepatic clearance of xanthine derivatives with an increase in the plasmatic levels of the drug.

Phenytoin, other anticonvulsants and cigarette smoking may increase the clearance of xanthine derivatives with a reduction of plasmatic half-life. In these cases, it may prove necessary to increase the dosage of the drug.

4.6. Pregnancy and lactation
Animal tests have shown that the active ingredient of ANSIMAR does not interfere with pre- and postnatal growth.

However, as there is not sufficient clinical evidence about the effects of the drug during pregnancy, use of the drug during pregnancy should be evaluated carefully case by case on the basis of the risk-benefit ratio. The drug is contraindicated during lactation.

4.7. Effects on ability to drive and use machines
The product does not affect the patient's alertness and therefore does not interfere with his/her ability to drive and use machines.

4.8. Undesirable effects
Patients treated with xanthine derivatives may suffer nausea, vomiting, epigastric pain, headache, irritability, insomnia, tachycardia, extrasystoles, tachypnea, and in rare cases, hyperglycemia or albuminuria. In case of overdose severe cardiac arrhythmias and tonic-clonic seizure may occur. These effects may represent the first signs of intoxication.

The appearance of side effects may require discontinuation of the treatment which, if necessary, at the physician's discretion, may be resumed at lower doses after all signs and symptoms of toxicity have subsided.

4.9. Overdose
As there is no specific antidote, in case of overdose a symptomatic treatment of cardiovascular collapse should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Doxofylline directly relaxes the smooth muscles of the bronchi and pulmonary vessels. In this way, it acts mainly as a bronchodilator, pulmonary vasodilator and as a relaxant of the bronchial muscle. The action of Doxofylline may be mediated, at least in part, by inhibition of the phosphodiesterase leading to an increase in intracellular cyclic AMP which results in smooth-muscle relaxation.
At higher concentrations, Doxofylline may inhibit the release of histamine by the cells.
Prolonged use of the drug does not lead to addiction.

5.2. Pharmacokinetic properties
Doxofylline half-life is more than 6 hours, so constant effective plasma levels may be maintained with three administrations a day.
The kinetics after a single i.v. and oral administration have been studied in man to define the distribution and absorption of the drug.
After intravenous administration of 100 mg of Doxofylline to 5 volunteers, the distribution of the unchanged substance in the serum follows a bi-compartmental model.
The area under the curve of the concentration of the drug in the serum during the distribution phase represents a small fraction of the total area.

Plasmatic clearance is high, with values ranging from 444 to 806 ml/min, whereas distribution volume is about 1 l/kg.

The mean half-life after intravenous administration was calculated to be 65 minutes (from 40 to 96).

After tablet administration, peak plasma levels are reached after 60 minutes, while with the syrup, due to its water and alcohol vehicle, the drug is absorbed more quickly, peak plasma concentration occurring within 30 minutes.

Absolute oral bioavailability is about 62.6%; at pH 7.4 the percentage of product bonded to the plasma proteins is about 48% .
Less than 4% of the oral dose is eliminated unchanged in the urine.

5.3. Preclinical safety data

Acute toxicity
The LD50 in rats and mice following oral, intraperitoneal and intravenous administration of the drug:

Oral administration:	in the rat	= 1022.4 mg/kg
	in the mouse	= 841.0 mg/kg
Intraperitoneal administration:	in the rat	= 444.7 mg/kg
Intravenous administration:	in m. rats	= 360 mg/kg
	in f. rats	= 310 mg/kg
	in m. mice	= 245 mg/kg
	in f. mice	= 238 mg/kg

Oral and i.p. acute toxicity in beagle dogs
Oral administration: over 800 mg/kg
I.p. administration : 400 mg/kg

Subacute toxicity (three months) - per os
In male and female rats at doses of:
7.21 mg/kg - 57.66 mg/kg - 288.40 mg/kg per os;

in male rats at doses of:
3.625 mg/kg - 29 mg/kg - 145 mg/kg i.p.;

in female rats at the dose of:
3.625 mg/kg i.p.;

in male and female beagle dogs at doses of:
180 mg/kg - 60 mg/kg - 20 mg/kg per os

no appreciable changes were observed.

Chronic toxicity (six months) -
In male rats at doses of:
7.21 mg/kg - 57.66 mg/kg - 288.4 mg/kg per os;

in female rats at doses of:
7.21 mg/kg - 288.4 mg/kg per os;

in male rats at doses of:
3.625 mg/kg - 29 mg/kg - 145 mg/kg i.p.;

in female rats at the dose of:
145 mg/kg i.p.;

in male and female beagle dogs, at doses of:
180 mg/kg - 60 mg/kg - 20 mg/kg

the product was well tolerated and had no toxic effects.

Subacute toxicity (1 month) - i.v.
In male and female rabbits at doses of:
57.68 mg/kg - 28.84 mg/kg - 7.21 mg/kg i.v.

the product proved suitable for prolonged i.v. administration.

The product was found to be free of fetal toxicity following tests carried out on rats and rabbits at the following doses:

- in rats: 57.66 mg/kg per os
  29 mg/kg i.p.

- in rabbits: 7.21 mg/kg - 28.84 mg/kg - 115.36 mg/kg via oral route.

The product was found to have no effect on fertility, pre or post-natal growth and no teratogenic effect on rats.

Doxofylline was also found to have no mutagenic effect**.**

6) PHARMACEUTICAL PARTICULARS

6.1. List of excipients

400 mg tablets
Lactose monohydrate, microcrystalline cellulose and sodium carboxymethyl cellulose, pre-gelled corn starch, anhydrous colloidal silica, hydrated colloidal silica, talc, magnesium stearate, Povidone K30

Ampoules
Distilled water.

Sachets for pediatric use
Sucrose, ammonium glycyrrhizinate, peppermint oil.

Syrup
Sucrose, ethyl alcohol, methyl p-hydroxybenzoate, peppermint oil, ammonium glycyrrhizinate, purified water.

6.2. Incompatibilities
No incompatibility with other substances has been reported for any of the available pharmaceutical forms.

6.3. Shelf-life

400 mg tablets:	60 months
Ampoules:	36 months
Sachets for pediatric use:	36 months
Syrup:	5 years

6.4. – Special precautions for storage
The preparation must be stored " at ordinary environmental conditions" as laid down by F.U.IX Ed.

6.5. - Nature and contents of container
ANSIMAR 400 mg tablets:
the tablets are packed in coupled PVC and aluminum foil blister packs, contained in a lithographed cardboard box, together with the package leaflet.
Box with twenty 400 mg tablets

ANSIMAR ampoules:
the ampoules, made of neutral, hydrolytic class 1 glass, are fitted into a thermoformed plastic tray inserted into a lithographed rigid cardboard box, together with the package leaflet.
Box with three 100 mg/10 ml ampoules

ANSIMAR sachets for pediatric use:
the sachets, made of polythene-coated aluminum, are contained, together with the package leaflet, in a lithographed rigid, cardboard box.
Box with twenty 200 mg sachets.

ANSIMAR syrup:
the syrup is contained in a brown glass bottle, closed with childproof cap, with an incorporated measuring cap.
The bottle is contained, together with the package leaflet and a 20 ml graduated measure, in a lithographed rigid cardboard box.
Bottle with 200 ml 2% syrup

6.6. Instructions for use and handling
No particular precautions need be taken in handling the product. See Posology and method of administration.

7. MARKETING AUTHORIZATION HOLDER
ABC FARMACEUTICI S.P.A.
CORSO VITTORIO EMANUELE II, 72
10121 TURIN

8. MARKETING AUTHORIZATION NUMBER(S)

ANSIMAR 20 tablets	code No.025474014
ANSIMAR 3 i.v. ampoules	code No.025474040
ANSIMAR 20 sachets	code No.025474038
ANSIMAR syrup	code No.025474065

9. DATE OF FIRST AUTHORIZATION

ANSIMAR 20 tablets:	30/10/84
ANSIMAR 3 i.v. ampoules:	30/10/84
ANSIMAR 20 sachets:	30/10/84
ANSIMAR syrup :	27/04/91

10. DATE OF REVISION OF THE TEXT March 2011