

Medicinal product no longer authorised

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ACOMPLIA 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg rimonabant.

Excipients:

The tablets contain approx. 115 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Biconvex, teardrop-shaped, white tablets debossed with "20" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As an adjunct to diet and exercise for the treatment of obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight patients ($\text{BMI} > 27 \text{ kg/m}^2$) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia (see section 5.1).

4.2 Posology and method of administration

In adults, the recommended dosage is one 20 mg tablet daily to be taken in the morning before breakfast.

The treatment should be introduced with a mildly reduced calorie diet.

The safety and efficacy of rimonabant have not been evaluated beyond 2 years.

- Special Populations

Elderly:

No dosage adjustment is required in elderly (see section 5.2). ACOMPLIA should be used with caution in patients over 75 years of age (see section 4.4).

Patients with hepatic insufficiency:

No dosage adjustment is required for patients with mild or moderate hepatic impairment. ACOMPLIA should be used with caution in patients with moderate hepatic impairment. ACOMPLIA should not be used in patients with severe hepatic impairment (see section 4.4 and 5.2).

Patients with renal impairment:

No dosage adjustment is required for patients with mild and moderate renal impairment (see section 5.2). ACOMPLIA should not be used in patients with severe renal impairment (see section 4.4 and 5.2).

Paediatrics:

ACOMPLIA is not recommended for use in children below age 18 due to a lack of data on efficacy and safety.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

Lactation.

Ongoing major depressive illness and/or ongoing antidepressive treatment (see section 4.4)

4.4 Special warnings and precautions for use

- *Depressive disorders*

Depressive disorders or mood alterations with depressive symptoms have been reported in up to 10%, and suicidal ideation in up to 1%, of patients receiving rimonabant (see section 4.8). In patients with current suicidal ideations and/or with a history of suicidal ideation and depressive disorder rimonabant should not be used unless the benefits of treatment are considered to outweigh these risks in an individual patient. (See section 4.3 and 4.8). Obesity is a condition that can be associated with depressive disorders. Depressive disorders can be associated with an increased risk of suicidal thoughts, self harm and suicide.

The prescriber should carefully investigate if the patient has had a depressive disorder in the past in order to evaluate the potential risks with rimonabant treatment.

Depressive reactions may occur in patients who have no obvious risk factors, apart from obesity itself. In postmarketing experience, more than half of the patients who develop such reactions appear to do so within 1 month of starting treatment, approximately 80% appear to do so within 3 months. Patients should be actively monitored for signs and symptoms of psychiatric disorders, particularly depression following the start of treatment. If depression is diagnosed during rimonabant therapy, rimonabant treatment must be stopped. The patient should be monitored and treated appropriately.

Patients, especially those with a history of depressive disorders/mood alterations, (and relatives or other relevant persons) should be alerted about the need to monitor for the emergence of such symptoms and to seek medical advice immediately if these occur.

- *Other psychiatric conditions*

Therapy with rimonabant is not recommended in patients with uncontrolled psychiatric illness. If psychiatric illness is diagnosed during rimonabant therapy, treatment must be stopped.

- *Seizures*

Rimonabant has not been studied in patients being treated for epilepsy. In clinical trials no difference in the incidence of seizures was seen in patients receiving rimonabant or placebo. Rimonabant, however, should be used with caution in these patients, see also section 5.3.

- *Hepatic impairment*

Rimonabant is metabolised by the liver, thus caution is advised in patients with moderate hepatic impairment. The pharmacokinetics and safety of rimonabant have not been studied in patients with severe hepatic impairment; its use in these patients is not recommended.

- *Renal impairment*

There are limited data in patients with moderate renal impairment and no data in patients with severe renal impairment. Rimonabant should not be used in patients with severe renal impairment (see section 4.2 and 5.2).

- *Elderly*

The efficacy and safety of rimonabant treatment in patients over 75 years of age has not sufficiently been established. Rimonabant should be used with caution in this population (see section 5.2).

- *Race*

The clinical effect (weight loss) of rimonabant in Black patients was lower than in Caucasians. This could be caused by a higher rimonabant clearance than in Caucasians resulting in a lower exposure (see section 5.2).

- *Diabetic patients*

Due to the effect of rimonabant on the blood glucose level, when rimonabant is administered in diabetic patients, hypoglycaemia can occur (see section 4.8). Monitoring of blood glucose level is recommended in these patients.

- *Drug Interaction*

Rimonabant should be used with caution in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, nefazodone)(see section 4.5).

- *Lactose*

Since ACOMPLIA tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

Patients should be instructed not to increase their dose of ACOMPLIA.

Patients who had a cardiovascular event (myocardial infarction, stroke, etc.) less than 6 months ago were excluded in the studies for rimonabant.

4.5 Interaction with other medicinal products and other forms of interaction

Rimonabant is metabolized by both CYP3A and amidohydrolase (predominantly hepatic) pathways *in vitro*. Concomitant administration of CYP3A4 inhibitors will lead to increased exposure of rimonabant. Concomitant administration of CYP3A4 inducers is expected to reduce the exposure of rimonabant.

Potential for other medicinal products to affect rimonabant:

Concomitant administration of ketoconazole (a potent CYP3A4 inhibitor) increased rimonabant AUC by 104% (95% prediction interval: 40% - 197%). A similar increase in exposure is expected with other potent CYP3A4 inhibitors. Caution is advised during concomitant use of ACOMPLIA and potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, nefazodone).

Although concomitant administration of CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St John's wort) has not been studied, it is expected that concomitant administration of potent CYP3A4 inducers may reduce the plasma concentration of rimonabant and may result in loss of efficacy.

Concomitant administration of orlistat, ethanol or lorazepam had no significant effect on the plasma levels of rimonabant.

Potential for rimonabant to affect other medicinal products:

The *in vivo* inhibitory effect on CYP2C8 has not been studied. However, *in vitro*, rimonabant had a mild inhibitory effect on CYP2C8. The potential for inhibition of CYP2C8 *in vivo* appears to be low. Rimonabant does not inhibit or induce other CYP enzymes or P-glycoprotein (P-gp) *in vitro*. This was confirmed clinically with specific probe studies using midazolam (CYP 3A4 substrate) and warfarin (CYP 2C9 substrate) and digoxin (a P-gp substrate).

The steady-state pharmacokinetics of an ethinyl estradiol/levonorgestrel combination oral contraceptive were not significantly altered by concomitant administration of rimonabant.

4.6 Pregnancy and lactation

There are no adequate or well-controlled studies in pregnant women. Animal data are inconclusive but suggest possible deleterious effects on embryonal/foetal development (see section 5.3). The potential risk for humans is unknown. Use in pregnancy is, therefore, not recommended. Patients should notify their physician if they become pregnant during treatment with ACOMPLIA.

Rimonabant has been detected in the milk of lactating rats and rimonabant may inhibit the suckling reflex. It is not known if rimonabant is excreted in human milk. ACOMPLIA is contraindicated during breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Cognitive investigations in clinical pharmacology studies demonstrated that rimonabant is devoid of any significant cognitive or sedative effect.

4.8 Undesirable effects

ACOMPLIA 20 mg has been evaluated for safety in approximately 2500 patients enrolled in studies that examined the metabolic and weight loss effects in overweight and obese patients and in approximately 3800 patients in other indications. In placebo-controlled studies, the discontinuation rate due to adverse reactions was 15.7% for patients receiving rimonabant. The most common adverse reactions resulting in discontinuation were: nausea, mood alteration with depressive symptoms, depressive disorders, anxiety and dizziness.

Depressive disorders were reported in 3.2% of obese patients, or overweight patients with associated risk factor(s) treated with rimonabant 20 mg. These were usually mild or moderate in severity and resulted in recovery in all cases either after corrective treatment or discontinuation of rimonabant and did not exhibit any differentiating characteristics compared to cases reported in the control groups.

The following table (table 1) shows all treatment-emergent adverse reactions from placebo-controlled studies in patients treated for weight loss and related metabolic disorders when these incidences were statistically significantly greater than the corresponding placebo rate (for events $\geq 1\%$) or considered clinically relevant (for events $< 1\%$).

Classification of expected frequencies of undesirable effects:

Very common ($\geq 10\%$); Common ($\geq 1, < 10\%$); Uncommon ($\geq 0.1, < 1\%$); Rare ($\geq 0.01, < 0.1\%$); Very rare ($< 0.01\%$), Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1:

System Organ Class	Very common	Common	Uncommon	Rare
Infections and infestations	Upper respiratory tract infection	Gastroenteritis		
Metabolism and nutrition disorders			Hypoglycaemia*	
Psychiatric disorders		Depressive disorders Mood alterations with depressive symptoms Anxiety Irritability Nervousness Sleep disorders Insomnia Parasomnias	Panic symptoms Anger Dysphoria Emotional disorder Suicidal ideation Aggressiveness Aggressive behaviour	Hallucinations
Nervous system disorders		Memory loss Dizziness Hypoaesthesia Sciatica Paresthesia	Lethargy Tremor	
Vascular disorders		Hot flush		
Respiratory, thoracic and mediastinal disorders			Hiccups	
Gastrointestinal disorders	Nausea	Diarrhoea Vomiting		
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis	Night sweats	
Musculoskeletal and connective tissue disorders		Tendonitis Muscle cramp Muscle spasms		
General disorders		Asthenia/fatigue Influenza		
Injury, Poisoning and procedural complications		Fall Contusion Joint sprain		

*frequency is based only on reports in obese or overweight diabetic patients.

In clinical studies for other indications, the following additional adverse reactions were commonly reported:

- infections and infestations: sinusitis
- metabolism and nutrition disorders: anorexia, decreased appetite,
- gastrointestinal disorders: stomach discomfort, dry mouth.

Post-Marketing

In addition the following adverse reactions were reported during postmarketing (frequency not known):

- Psychiatric disorder: psychotic disorders including hallucinations, delusion and paranoia.
- Skin and subcutaneous tissue disorders: rash.
- Nervous disorders: convulsions, disturbance in attention, headache.
- gastrointestinal disorders: abdominal pain.

Laboratory adverse events

ACOMPLIA has not been shown to alter laboratory test values.

4.9 Overdose

Experience with rimonabant in overdosage is limited. In a single-dose tolerability study, doses up to 300 mg were administered to a limited number of subjects with only minor symptoms reported. These included headache, euphoria, fatigue and insomnia. The pharmacokinetic profile demonstrates that a plateau in exposures is reached at 180 mg. There is no specific antidote for rimonabant; therefore, appropriate supportive measures should be initiated in case of overdose. Treatment should consist of the general measures employed in the management of overdoses, such as keeping airways unobstructed, monitoring cardiovascular function and general symptomatic and supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Anti obesity agent

ATC code: A08AX01

Rimonabant is a selective cannabinoid-1 receptor (CB1) antagonist that inhibits the pharmacological effects of cannabinoid agonists *in vitro* and *in vivo*.

The endocannabinoid system is a physiological system present in brain and peripheral tissues (including adipocytes) that affects energy balance, glucose and lipid metabolism and body weight, and in neurons of the mesolimbic system modulates the intake of highly palatable, sweet or fatty foods.

Clinical study results

Weight Management

In total more than 6800 patients were included in the Phase 2 and Phase 3 clinical studies. The patients included in the phase 3 trials followed a restrictive diet during the trial prescribed by a dietician and they were advised to increase their physical activity. Patients had a BMI ≥ 30 kg/m² or BMI > 27 kg/m² with hypertension and/or dyslipidemia at inclusion. Approximately 80% of the population were women, 87% Caucasian and 9% Black. Experience in patients over 75 years and Orientals/Asians was limited.

Significant mean weight reductions from baseline to one year for ACOMPLIA 20 mg versus placebo were demonstrated in three studies conducted in non-diabetic patients. A mean weight loss of 6.5 kg from baseline to one year was shown for ACOMPLIA 20 mg versus a mean weight loss of 1.6 kg for placebo (Difference -4.9 kg CI_{95%} -5.3;-4.4, $p < 0.001$).

The percentage of patients who lost 5% and 10% of their baseline body weight after 1 year of treatment are given in table 2:

Table 2:

	Non-diabetic studies		Diabetic study	
	Placebo	ACOMPLIA 20 mg	Placebo	ACOMPLIA 20 mg
n _{ITT}	1254	2164	348	339
Weight at baseline (kg)	101	101	96	95
Subjects with a 5% weight reduction	19.7%	50.8%	14.5%	49.4%
Difference (CI _{95%})	31.1% (28%; 34%)		34.9% (28%; 41%)	
Subjects with a 10% weight reduction	7.8%	27.0%	2.0%	16.2%
Difference (CI _{95%})	19.2% (17%; 22%)		14.2% (10%; 19%)	

Most of the observed weight reduction was obtained within the first nine months of treatment. ACOMPLIA 20 mg was effective in maintaining weight loss up to two years. Weight loss at two years was 5.1 kg for patients who received ACOMPLIA 20 mg and 1.2 kg for placebo (Difference -3.8 kg; CI_{95%} -4.4, -3.3; p< 0.001).

Rimonabant 20 mg reduced the risk of weight regain. Patients who received ACOMPLIA 20 mg for one year were re-randomized to ACOMPLIA 20 mg or placebo. At two years, patients continuing on rimonabant had a mean total weight loss of 7.5 kg over 2 years whereas patients re-randomized to placebo group during the second year had a mean total weight loss of 3.1 kg over 2 years. At two years, the difference in total weight loss between ACOMPLIA and placebo was -4.2 kg (CI_{95%} -5.0; -3.4, p< 0.001).

Treatment with rimonabant was associated with significant reductions in waist circumference, a known marker of intra-abdominal fat.

The effects on body weight appeared to be consistent among men and women. In the limited number of Black patients weight loss was less pronounced (mean difference to placebo -2.9 kg). No conclusions can be drawn with regard to effects in patients over 75 years or in Asian/Oriental patients due to the low number of patients.

Weight management and additional risk factors

In the non-diabetic studies including a mixed population of subjects with/without (treated) dyslipidemia, an increase in HDL-C and decrease in triglycerides (at one year) was observed. For HDL-C an average increase of 16.4% was seen under rimonabant 20 mg (baseline HDL-C 1.24 mmol/l) compared to an increase of 8.9% for placebo (baseline HDL-C 1.21 mmol/l). The difference was statistically significant (Difference 7.9% CI_{95%} 6.6%; 9.2%, p< 0.001). For the triglycerides an average decrease of 6.9% was seen under rimonabant 20 mg (baseline TG 1.62 mmol/l) compared to an increase of 5.8% for placebo (baseline TG 1.65 mmol/l). The difference was statistically significant (Difference -13.3% CI_{95%} -16.5; -10.2% p< 0.001). It is estimated that approximately half of the observed improvement in HDL-C and triglycerides in patients who received rimonabant 20 mg was beyond that expected from weight loss alone.

Generally ACOMPLIA 20 mg had no significant effect on Total-C or LDL-C levels.

In the trial in type 2 diabetic patients (RIO-Diabetes) who were overweight or obese treated with metformin or sulfonylurea improvements in HbA1c and body weight were observed. The absolute change in HbA1c at one year was -0.6 for rimonabant 20 mg (baseline 7.3%) and +0.1 on placebo (baseline 7.2%). Differences were statistically significant (Difference -0.7%, CI_{95%} -0.80; -0.5, p<0.001).

At one year a mean weight loss of 5.3 kg was shown for ACOMPLIA 20 mg versus a loss on placebo of 1.4 kg (Difference -3.9 kg CI_{95%} -4.6;-3.3 p<0.001). The percentage of patients who lost 5% and 10% of their baseline body weight after 1 year of treatment are given in the table 2.

In a second trial in treatment naïve type 2 diabetic obese patients (Serenade), the absolute change in HbA1c (with a baseline of 7.9% for both groups) at six months was -0.8 for rimonabant 20 mg and -0.3 under placebo (Difference -0.51 CI_{95%} -0.78, -0.24 p< 0.001). The percentage of patients reaching HbA1c < 7% was 51% in the rimonabant group and 35% in the placebo group. The difference in mean body weight change between the 20 mg and placebo groups was 3.8 kg (CI_{95%} -5.0, -2.6 p< 0.001). Changes in HDL-C and TG in this population were similar to that of the non-diabetic population. It is estimated that approximately half of the mean improvement in HbA1c in patients receiving rimonabant 20 mg was beyond that expected from weight loss alone.

5.2 Pharmacokinetic properties

Rimonabant pharmacokinetics are fairly dose proportional up to about 20 mg. AUC increased less than in proportion to dose above 20 mg.

Absorption:

Rimonabant displays high *in vitro* permeability and is not a substrate of P-glycoprotein. The absolute bioavailability of rimonabant has not been determined. Following multiple once-daily doses of 20 mg to healthy subjects in the fasted state, maximum plasma concentrations of rimonabant are achieved in approximately 2 hours with steady state plasma levels achieved within 13 days ($C_{max} = 196 \pm 28.1$ ng/ml; $C_{trough} = 91.6 \pm 14.1$ ng/ml; $AUC_{0-24} = 2960 \pm 268$ ng.h/ml). Steady state rimonabant exposures are 3.3-fold higher than those observed after the first dose. Population pharmacokinetic analysis demonstrated less fluctuation in peak to trough plasma concentration but no differences in steady state AUC as weight increases. As weight increases from 65 to 200 kg, C_{max} is expected to decrease 24% and C_{trough} is expected to increase by 5%. Time to steady state is longer in obese patients (25 days) as a consequence of the higher volume of distribution in these patients. Population pharmacokinetic analysis indicated that rimonabant pharmacokinetics are similar between healthy non-smoking subjects and patients who smoke.

Effect of food:

Administration of rimonabant to healthy subjects in the fasted state or with a high fat meal demonstrated that C_{max} and AUC were increased 67% and 48% respectively, under fed conditions. In clinical studies, ACOMPLIA 20 mg was taken in the morning usually before breakfast.

Distribution:

The *in vitro* human plasma protein binding of rimonabant is high (> 99.9%) and non-saturable over a wide concentration range. The apparent peripheral volume of distribution of rimonabant appears to be related to body weight, with obese patients having a higher volume of distribution than normal-weight subjects.

Biotransformation:

Rimonabant is metabolized by both CYP3A and amidohydrolase (predominantly hepatic) pathways *in vitro*. Circulating metabolites do not contribute to its pharmacologic activity.

Elimination:

Rimonabant is mainly eliminated by metabolism and subsequent biliary excretion of metabolites. Only an approximate 3% of the dose of rimonabant is eliminated in the urine, while approximately 86% of the dose is excreted in the faeces as unchanged drug and metabolites. In obese patients, the elimination half-life is longer (about 16 days) than in non-obese patients (about 9 days) due to a larger volume of distribution.

Special Populations

Race:

In single- and repeat-dose studies, the C_{max} and AUC of rimonabant were similar in healthy Japanese and Caucasian subjects, whereas elimination half-life was shorter in Japanese subjects (3-4 days) compared to Caucasian subjects (about 9 days). The difference in half-life was due to differences in peripheral volume of distribution as a consequence of lower weight in Japanese subjects. Black patients may have up to a 31% lower C_{max} and a 43% lower AUC than patients of other races.

Gender:

The pharmacokinetics of rimonabant are similar in female and male patients.

Elderly:

Elderly patients have slightly higher exposure than young patients. Based on a population pharmacokinetic analysis (age range 18 - 81 years) a 75 year old patient is estimated to have a 21% higher C_{max} and a 27% higher AUC than a 40 year old patient.

Patients with hepatic insufficiency:

Mild hepatic impairment does not alter rimonabant exposure. Data are insufficient to draw conclusions regarding pharmacokinetics in moderate hepatic impairment. Patients with severe hepatic impairment were not evaluated.

Patients with renal impairment:

The effect of renal function on the pharmacokinetics of rimonabant has not been studied specifically. Based on data from population pharmacokinetic studies, mild renal impairment do not seem to affect the pharmacokinetics of rimonabant. Limited data suggest an increased exposure in patients with moderate renal impairment (40% increase in AUC). There are no data in severe renal impairment.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Convulsions were observed sporadically in studies in rodents and macaques. No convulsions were observed in dogs during a 3 month study. In some, but not all cases, initiation of convulsions appeared to be associated with procedural stress such as handling of the animals. A proconvulsant activity of rimonabant was found in one of two safety-pharmacology studies. No adverse effect of rimonabant treatment was observed on EEG patterns in rats.

Increased incidence and/or severity of clinical signs suggestive of increased tactile hyperesthesia were observed in rodent studies. A direct effect of rimonabant cannot be ruled out.

Liver steatosis and a dose-related increase in centrilobular necrosis were observed in long-term studies in the rat. A direct effect of rimonabant cannot be ruled out.

In standard fertility studies in female rats (dosing for 2 weeks prior to mating) there was abnormal oestrous cyclicity and a decrease in corpora lutea and fertility index at doses of rimonabant that induced maternal toxicity (30 and 60 mg/kg/day). Following dosing for a longer treatment duration prior to mating (9 weeks) that permitted recovery from the initial effects of rimonabant, no adverse effects were seen on fertility or oestrous cyclicity. Regarding reproductive parameters, at 30 mg/kg no differences were observed between treated animals and controls, at 60 mg/kg effects were still observed (decreased number of corpora lutea, implantations, total and viable fetuses).

Sporadic malformations (anencephaly, micro-ophthalmia, widened brain ventricles and omphalocele) were observed in the rabbit embryofetal toxicity studies at doses resulting in exposures comparable with the clinical exposures. Although maternal toxicity was observed at these doses, a relation to treatment cannot be excluded. No treatment-related malformations were seen in the rat.

Effects of rimonabant on pre- and post-natal development were assessed in the rat at doses up to 10 mg/kg/day. There was a treatment related increase in pup mortality in the pre-weaning period. The increased pup mortality might be attributable to a failure of the dam to nurse or ingestion of rimonabant in milk and/or inhibition of the suckling reflex that is reported in the literature to be initiated in neonatal mice by endocannabinoid signalling via CB1 receptors. There are reports in the literature that, in both rodents and humans, the spatial distribution and density of CB1 receptors in the brain changes during development. The potential relevance of this to administration of a CB1 antagonist is unknown. In the pre- and post-natal development study in rats, exposure to rimonabant in utero and via lactation produced no alterations on learning or memory, but equivocal effects on motor activity and auditory startle response were observed in the pups as a result of rimonabant exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
maize starch,
lactose monohydrate,
povidone K 30 (E1201),
croscarmellose sodium (E468),
sodium laurilsulfate (E487),
microcrystalline cellulose (E460),
magnesium stearate

Tablet coating:
lactose monohydrate,
hypromellose 15 mPa.s (E464),
titanium dioxide (E171),
macrogol 3000

Tablet polishing:
carnauba wax (E903)

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-aluminium blister packs containing 14, 28, 30, 56, 84, 90 and 98 film-coated tablets.
70 x 1 film-coated tablets in PVC-aluminium perforated unit dose blister packs.
Opaque white HDPE bottles containing 28, 98 and 500 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORIZATION HOLDER

sanofi-aventis.
174 Avenue de France
F-75013 Paris
France

8. MARKETING AUTHORIZATION NUMBER

EU/1/06/344/001-011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 June 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu>.

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

Medicinal product no longer authorised

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Sanofi Winthrop Industrie, 30-36 Avenue Gustave Eiffel, BP 27166, F-37071 Tours Cedex 2, France
sanofi-aventis S.p.A., Strada Statale 17, Km 22 , 67019 Scoppito (AQ), Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated risk management plan should be provided as per the CHMP guideline on risk management systems for medicinal products for human use.

Medicinal product no longer authorised

**ANNEX III
LABELLING AND PACKAGE LEAFLET**

Medicinal product no longer authorised

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for the presentations of 14, 28, 30 56, 70, 84, 90 and 98 film-coated tablets in blisters

1. NAME OF THE MEDICINAL PRODUCT

ACOMPLIA 20 mg film-coated tablets
rimonabant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg of rimonabant.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
70x1 film coated-tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis
174 avenue de France
F-75013 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/344/001
EU/1/06/344/002
EU/1/06/344/003
EU/1/06/344/004
EU/1/06/344/005
EU/1/06/344/006
EU/1/06/344/010
EU/1/06/344/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ACOMPLIA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters of the presentations of 14, 28, 56, 84 and 98 film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ACOMPLIA 20 mg film-coated tablets
rimonabant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters of the presentations of 30, 70 x 1 and 90 film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ACOMPLIA 20 mg film-coated tablets
rimonabant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

Carton of the presentations of 28, 98 and 500 film-coated tablets in HDPE bottles / HDPE bottle label for the presentations of 28, 98 and 500 film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ACOMPLIA 20 mg film-coated tablets
rimonabant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg of rimonabant.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
98 film-coated tablets
500 film-coated tablets

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis
174 avenue de France
F-75013 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/344/007
EU/1/06/344/008
EU/1/06/344/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ACOMPLIA

Medicinal product no longer authorised

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ACOMPLIA 20 mg film-coated tablets (rimonabant)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.
- You are advised to share the information in this leaflet with relatives or other relevant persons.

In this leaflet:

1. What ACOMPLIA is and what it is used for
2. Before you take ACOMPLIA
3. How to take ACOMPLIA
4. Possible side effects
5. How to store ACOMPLIA
6. Further information

1. WHAT ACOMPLIA IS AND WHAT IT IS USED FOR

The active ingredient of ACOMPLIA is rimonabant. It works by blocking specific receptors in the brain and fat tissues called CB1 receptors. ACOMPLIA is indicated in the treatment of obese or overweight patients with additional risk factors such as diabetes or high levels of fatty substances in the blood called lipids (dyslipidaemia; mainly cholesterol and triglycerides) as adjunct to diet and exercise.

2. BEFORE YOU TAKE ACOMPLIA

Do not take ACOMPLIA

- if you currently suffer from depression
- if you are currently being treated for depression
- if you are allergic (hypersensitive) to rimonabant, or any of the other ingredients of ACOMPLIA
- if you are breast-feeding

Take special care with ACOMPLIA

Tell your doctor before you start to take this medicine

- if you have previously suffered from depression or have had suicidal thoughts
- if you have impaired liver function
- if you have severely impaired renal function
- if you have diabetes (see section 4)
- if you are currently being treated for epilepsy
- if you are less than 18 years of age. There is no information available on the use of ACOMPLIA in people under 18 years of age.

Serious psychiatric events including depression or mood changes have been reported in patients taking ACOMPLIA (see section **POSSIBLE SIDE EFFECTS**).

If you experience symptoms of depression (see below) during treatment with ACOMPLIA you should contact your doctor and stop the treatment.

Signs and symptoms associated with depression could be:

Sadness, depressed mood; loss of interest in previously pleasurable activities; agitation; irritability; slowed, inhibited actions; poor concentration; anxiety; difficulty in sleeping (insomnia); thoughts or words about death or suicide.

You should inform your doctor if any of the symptoms listed above develop or worsen after treatment has begun.

Taking other medicines

The activity of ACOMPLIA is increased by simultaneous use of some drugs (so-called CYP3A4 inhibitors) such as:

- itraconazole (antifungal medicine)
- ketoconazole (antifungal medicine)
- ritonavir (medicine for the treatment of HIV infections)
- telithromycin (antibiotic)
- clarithromycin (antibiotic)
- nefazodone (anti-depressor)

Please inform your doctor or pharmacist if you are taking or have recently taken the above mentioned medicines or any other medicines, including those obtained without a prescription such as St John's wort, rifampicin (antibiotic), medicines for weight loss, medicines to improve blood lipids (fats), antidiabetes medicines and medicines to treat epilepsy (e.g. phenytoin, phenobarbital, carbamazepine) or depression.

Pregnancy and breast-feeding

ACOMPLIA should not be taken during pregnancy.

Contact your doctor immediately if you become pregnant, think you might be pregnant or are planning to become pregnant while taking ACOMPLIA.

Do not take this medicine when breast-feeding. Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby.

Driving and using machines

At the recommended dose, ACOMPLIA is not expected to reduce your ability to drive and use machines.

Important information about some of the ingredients of ACOMPLIA

ACOMPLIA tablets include lactose. If you are intolerant to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ACOMPLIA

Always take ACOMPLIA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one 20 mg tablet to be taken once daily in the morning before breakfast. Swallow the tablet whole.

You need to start and continue a reduced calorie diet and a physical activity program to get best results. Your doctor should recommend the type of diet and the level of physical activity required, that suits your specific condition and overall health.

Taking ACOMPLIA with food and drink

ACOMPLIA should be taken once daily in the morning before breakfast.

If you take more ACOMPLIA than you should

If you take more ACOMPLIA than you should tell a doctor or pharmacist.

If you forget to take ACOMPLIA

Take it as soon as you remember but do not take a double dose to make up for any forgotten dose.

If you have any further questions on the use of this product ask your doctor or your pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ACOMPLIA can cause side effects, although not everybody gets them

Very common side effects, that affect more than 1 per 10, that have occurred in patients on ACOMPLIA include:

nausea and upper respiratory tract infection.

Common side effects, that affect more than 1 per 100 but less than 1 per 10, that have occurred in patients on ACOMPLIA include:

upset stomach, vomiting, trouble with sleeping, nervousness, depression, irritability, dizziness, diarrhoea, anxiety, itching, excessive sweating, muscle cramps or spasm, fatigue, bruising, tendon pain and inflammation (tendonitis), memory loss, back pain (sciatica), altered sensitivity (less sensitivity or abnormal burning or prickling sensation) of the hands and feet, hot flush, fall, influenza, and joint sprain.

Uncommon side effects, that affect less than 1 per 100 but more than 1 per 1000, that have occurred in patients on ACOMPLIA include:

Sleepiness (lethargy), tremor, night sweats, panic symptoms, hiccups, anger, restlessness (dysphoria), emotional disorder, suicidal thoughts, aggressiveness or aggressive behaviour, hypoglycaemia (low blood sugar).

Rare side effects, that affect less than 1 per 1000, that have occurred in patients on ACOMPLIA include: hallucinations.

During post-marketing experience the following side effects have also been reported (frequency not known):

Convulsion, disturbance in attention, delusion (false belief), paranoia, rash, headache and stomach pain.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ACOMPLIA

Keep out of the reach and sight of children.

Do not use ACOMPLIA after the expiry date which is stated on the outer packaging after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ACOMPLIA contains

The active substance is rimonabant. One film-coated tablet contains 20 mg rimonabant.

The other ingredients are:

Tablet core: maize starch, lactose monohydrate, povidone K 30 (E1201), croscarmellose sodium (E468), sodium laurilsulfate (E487), microcrystalline cellulose (E460), magnesium stearate

Tablet coating: lactose monohydrate, hypromellose 15 mPa.s (E464), titanium dioxide (E171), macrogol 3000

Tablet polishing: carnauba wax (E903)

What ACOMPLIA looks like and contents of the pack

ACOMPLIA 20 mg is supplied as teardrop-shaped, white film-coated tablets debossed with “20” on one side.

ACOMPLIA is available in blister packs of 14, 28, 30, 56, 84, 90 and 98 tablets, in perforated unit dose blister packs containing 70 x 1 tablets, and in white plastic bottles containing 28, 98 and 500 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

sanofi-aventis
174, avenue de France
F-75013 Paris
France

Manufacturers

Sanofi Winthrop Industrie
30-36, avenue Gustave Eiffel – BP 27166
F-37071 Tours Cedex 2
France

sanofi-aventis S.p.A.
Strada Statale 17, Km 22
67019 Scoppito (AQ)
Italy

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/ Belgique/ Belgien
sanofi-aventis Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: +49 (0)180 2 222010

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Ireland
sanofi-aventis Ireland Ltd.
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
sanofi-aventis S.p.A.
Tel: +39 02 393 91

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Luxembourg/Luxemburg
sanofi-aventis Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
sanofi-aventis zrt., Magyarország
Tel.: +36 1 505 0050

Malta
sanofi-aventis Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 -0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 541 46 00

Portugal
sanofi-aventis - Produtos Farmacêuticos, S.A.
Tel: +351 21 35 89 400

România
sanofi-aventis România S.R.L.
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 57 103 777

Suomi/Finland
sanofi-aventis Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
sanofi-aventis AB
Tel: +46 (0)8 634 50 00

United Kingdom
sanofi-aventis
Tel: +44 (0) 1483 505 515

Lietuva
UAB sanofi-aventis Lietuva
Tel: +370 5 2755224

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu>.

Medicinal product no longer authorised