# ANNEX I

## LIST OF THE NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDER, STRENGTHS, PHARMACEUTICAL FORM, ROUTE OF ADMINISTRATION, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

**SIBUTRAMINE CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN THE EUROPEAN UNION**

| Member State | Marketing Authorisation Holder | Product Name | Strength | Pharmaceutical Form | Route of administration | Packaging | Package size |
|---|---|---|---|---|---|---|---|
| **Germany** | Knoll Deutschland GmbH<br>Rathausplatz 10-12<br>67059 Ludwigshafen<br>Germany | Reductil 10 | 10 mg | capsule | oral | PVC/PVDC<br>blister strip pack | 28<br>56<br>98<br>280 |
| **Germany** | Knoll Deutschland GmbH<br>Rathausplatz 10-12<br>67059 Ludwigshafen<br>Germany | Reductil 15 | 15 mg | capsule | oral | PVC/PVDC<br>blister strip pack | 28<br>56<br>98<br>280 |
| **Germany** | Knoll Deutschland GmbH<br>Rathausplatz 10-12<br>67059 Ludwigshafen<br>Germany | Zelium 10 | 10 mg | capsule | oral | PVC/PVDC<br>blister strip pack | 28<br>56<br>98<br>280 |
| **Germany** | Knoll Deutschland GmbH<br>Rathausplatz 10-12<br>67059 Ludwigshafen<br>Germany | Zelium 15 | 15 mg | capsule | oral | PVC/PVDC<br>blister strip pack | 28<br>56<br>98<br>280 |
| **Germany** | Knoll Deutschland GmbH<br>Rathausplatz 10-12<br>67059 Ludwigshafen<br>Germany | Reduxade 10 | 10 mg | capsule | oral | PVC/PVDC<br>blister strip pack | 28<br>56<br>98<br>280 |
| **Germany** | Knoll Deutschland GmbH<br>Rathausplatz 10-12<br>67059 Ludwigshafen<br>Germany | Reduxade 15 | 15 mg | capsule | oral | PVC/PVDC<br>blister strip pack | 28<br>56<br>98<br>280 |

**ANNEX II**
**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA**

**SCIENTIFIC CONCLUSIONS**

**OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SIBUTRAMINE CONTAINING MEDICINAL PRODUCTS**

Sibutramine, an anti-obesity agent which inhibits the reuptake of norepinephrine and 5-hydroxitryptamine, was approved in Germany in January 1999 and subsequently applications were submitted in all Member States, except France, through a Mutual Recognition Procedure (MRP). In France a national application is pending.

During the MRP the majority of the Member States raised several objections with regard to the safety (cardiovascular risk, abuse potential) and efficacy of sibutramine. By day 85 of the MRP the majority of the Concerned Member States (Belgium, Denmark, Greece, Ireland, Luxembourg, Netherlands, Sweden and the United Kingdom) considered that sibutramine had an unfavourable benefit/risk and consequently the Applicant withdrew the application in these Member States before day 90. By day 90 of the MRP only four Member States (Austria, Finland, Italy and Portugal) were ready to grant the Marketing Authorisations.

Belgium considered that sibutramine gave rise to increased blood pressure and heart rate in a substantial number of users and that the long-term consequences of these effects were not sufficiently documented in the MRP application dossier. Belgium considered that this was a matter of major concern since obese patients have already an increased risk for cardiovascular disease. Furthermore the efficacy of sibutramine was considered doubtful. Therefore, for these two reasons - increased cardiovascular risk and a disputable efficacy - on 4 October 1999 Belgium triggered a referral to the EMEA under Article 12 of Council Directive 75/319/EEC as amended, requesting the CPMP to reassess the benefit/risk of sibutramine containing medicinal products.

**EFFICACY**

**Long-term weight loss and weight maintenance**

Evidence of long-term weight reduction and weight maintenance of at least 12 months in obese patients was provided in six placebo-controlled, double blind, parallel-group studies (SB1047, SB1048, SB1049, KD9618, SB5078 and SB6085). Three of the six clinical trials aimed to prove efficacy of sibutramine in inducing weight loss in unselected populations (the majority of patients enrolled have co-morbid conditions: dyslipidaemia -75%- and hypertension -19%-, one was conducted in obese non-diabetic patients -SB1047- and two others in obese patients with type II diabetes -SB 5078 and SB 6085). Study KD9618 aimed to prove efficacy of sibutramine in inducing weight loss in a population of obese patients that showed to be responders to 15 mg of sibutramine in a run-in phase with a duration of 1 month. Finally, sibutramine ability to maintain weight loss induced by sibutramine itself was assessed in one study (SB1048) and the ability to maintain and/or induced further weight loss after 1 month of very low calorie diet (VLCD) was assessed in other study (SB 1049).

The general characteristics of these trials were as follows:
Inclusion criteria: BMI ≥ 27 kg/$m^2$. Actual range 25.2 - 58.6 kg/$m^2$

Efficacy criteria: the primary efficacy criteria was change in body weight; in the case of the maintenance trial (SB 1048) the primary efficacy criteria was successful weight maintenance defined as maintaining ≥ 80% of total weight loss between baseline and month 6 to endpoint; the secondary efficacy criteria were related to obesity risk factors: lipid profiles, glycaemic control, total body fat and abdominal visceral fat, uric acid, quality of life.

Safety criteria: undesirable effects related with the sympaticomimetic actions of sibutramine such as hypertension and increased heart rate. Left ventricular mass (1 study) laboratory assessments of routine test organ's function.
Non-pharmacological measures: general dietary advice concerning healthy eating and calorie reduction; in study SB 1048 and SB 5078 there were an individualised diet (600 and 700 Kcal deficit respectively) and an exercise plan in study SB 1048. In study SB 1049, in the initial phase, a VLCD was instituted (220-800 kcal/day) and afterwards there was an individualised diet inferior to 1500 Kcal/day.
It should be noted that, in the majority of the 6 clinical trials, the counselling regarding diet and exercise was done in a rather general way and was not really standardised. Adherence to these recommendations was not always documented satisfactorily. Thus, it is not clear if the potential benefit of the non-pharmacological strategies were really exhausted in the population enrolled in the trials. However these concerns are mostly

resolved by the results of study SB 1049 where a run-in period with a controlled dietary regimen of a VLCD was implemented and patients were forced to achieve a target weight loss of at least 6 kg before starting pharmacological treatment.

These studies satisfied current requirements to include both the effects of treatment on acute weight loss and the efficacy of the drug therapy on the maintenance of weight loss or the prevention of weight regain after the plateau in weight has been reached, as recommended in the Note for Guidance on Clinical Investigation of Drugs Used in Weight Control – CPMP/EWP/281/96. Overall, 1344 obese patients received sibutramine at the recommended doses (595 received sibutramine 10 mg and 749 sibutramine 15 mg) of whom 346 (59%) and 572 (76%) completed at least 12 months therapy with sibutramine 10 mg or 15 mg, respectively. 743 patients received placebo, of whom 485 (65%) completed 12 months.

In these studies the following results regarding mean weight loss at end-point were obtained (see table 1):

Table 1 – Results from long-term studies with regard to mean weight loss at end point

| Variable | Study | Sibutramine 10 mg (mean weight loss at end-point – kg) | Sibutramine 15 mg (mean weight loss at end-point – kg) | Placebo (mean weight loss at end-point – kg) | P value |
|---|---|---|---|---|---|
| Mean weigh loss at end-point (kg) | SB1047 | -4.4 | -6.4 | -1.6 | <0.01 |
| | SB1048⇓ | -9.3 | ----- | -5.3 | <0.001 |
| | SB1049∨ | -12.8 | ---- | -5.2 | <0.001 |
| | KD 9618 | | -7.9 | -3.8 | <0.001 |
| | SB5078** | | -7.1 | -2.6 | <0.001 |
| | SB6085** | | -5.5 | -0.2 | <0.001 |
| | Mean of the means* | -7.6±2.8 | | -3.1±2.0 | |

*a very crude estimate of the overall effect
⇓ maintenance study ( end-point at 2 years)
** type II diabetes
∨ initial phase: VLCL

From these studies it can be concluded that sibutramine is effective in reducing body weight in a certain group of patients. The study SB 1049 is an outliner in the group and this should be taken into consideration because it emphasises the need for combining well implemented non-pharmacological measures to achieve a meaningful effect. Furthermore the analysis of the studies in diabetic patients shows that the decrease of weight loss is slower than in the non-diabetic patients. This is a very crude analysis because the design of the trials is not exactly the same. However, study SB 1047 is reasonably similar, in what concerns design, to the trials in diabetics. In spite of this slowness the effect size at end-point is of the same order of magnitude in diabetics and non-diabetics.

Weight regain occurred after stopping active treatment with sibutramine. However, there was no active non-pharmacological intervention after the end of the studies, which should not happen in the clinical setting.

In the 6 long-term clinical trials the percentage of 5% responders, relative to placebo, varied between 18% and 48% and the percentage of 10% responders, relative to placebo, varied between 25 and 31%. The frequency of distribution of 10% responders at end-point, in comparison with placebo, is reported in the table below (table 2). According with the figures in the table the mean percentage of 10% responders was 34.6% for sibutramine 10 mg, 30% for sibutramine 15 mg and 11.3% for placebo. The actual numbers were calculated from the percentages given for each study and the corresponding totals of patients included (ITT – intention to treat dataset - population).

Table 2

| STUDIES | Sibutramine 10mg | | Sibutramine 15mg | | Placebo | |
|---|---|---|---|---|---|---|
| | R.10%(n) | Total | R.10%(n) | Total | R.10%(n) | Total |
| SB1047 | 31 | 161 | 55 | 161 | 11 | 163 |
| SB1048 | 131 | 350 | ---- | ---- | 22 | 114 |
| SB1049 | 43 | 82 | ---- | ---- | 18 | 78 |
| KD9618 | ---- | ---- | 131 | 405 | 27 | 201 |

| | | | | | | |
|---|---|---|---|---|---|---|
| SB5078 | ---- | ---- | 31 | 114 | 6 | 122 |
| SB6085 | | | 10 | 69 | 0 | 64 |
| **TOTALS** | **205** | **593** | **227** | **749** | **84** | **742** |
| | **34.6%** | | **30.0%** (31.2%) | | **11.3%** (14%) | |

From the analysis of the available data it can be concluded that sibutramine is effective with regard to weight loss. The magnitude of the effect expressed as mean weight loss is modest, but the number of 10% responders is acceptable. In the CPMP Note for Guidance on Clinical Investigation of Drugs Used in Weight Control (CPMP/EWP/281/96) 10% weight loss is considered as a therapeutically meaningful target in obesity. Therefore the efficacy of sibutramine as a weight reducing substance in long-term treatment (12 months) is supported.
For longer than 12 months the only data available is the one from the study SB 1048 where it is shown that the use of sibutramine increases the likelihood of maintaining the previous induced weight loss.

**Potential clinical consequences after long-term weight loss and weight maintenance**

The potential clinical consequences of intentional weight loss and weight maintenance includes improvements in obesity-related co-morbidities (such as dyslipidemia and diabetes mellitus) and cardiovascular risk factors such as total body fat and abdominal visceral fat, uric acid. The effect of long-term sibutramine treatment on these variables is considered below.

Lipid profiles

A meta-analysis of an effect on lipid profiles of patients in the six trials was provided by the MAH and considered by the CPMP. At least 75% of the patients in both treatment groups were dyslipidaemic at baseline.

Improvements in triglycerides and HDL-cholesterol accompanied the sibutramine-induced weight loss when compared with placebo. More substantial beneficial effects are evident in those patients who lose clinically significant amounts of weight, i.e. ≥5% and ≥10% from baseline and the improvement in serum lipids was commensurate with the degree of weight loss induced by sibutramine. Consistent trends are also seen in LDL-cholesterol.

In conclusion the available data suggests that sibutramine use has a beneficial effect over the lipid profile in the patients that are 10% responders. Besides the favorable data on triglycerides and HDL, study SB 5078 provides data on apolipoproteins fractions A1 and B which emphasis the improvement in the lipid profile induced by sibutramine.

Glycaemic control

As already presented, two 12-month, prospective studies were conducted in obese patients with type 2 diabetes mellitus (in SB5078, the patients were controlled by diet alone and in SB6085, by a stable dose of metformin). An additional study in type 2 diabetic patients has been completed (SB5075: patients controlled by a stable dose of an oral sulphonylurea).

In these studies patients treated with sibutramine had reductions in HbA1c that were both clinically and metabolically significant. Greater improvement in $HbA_{1c}$ resulted from greater weight loss. In long-term clinical trials, sibutramine given concomitantly with metformin (SB6085) or sulphonylurea (SB5075) has been demonstrated to reduce fasting blood glucose levels by up to 1.9 mmol/l and reduce $HbA_{1c}$ levels between 0.9 and 2.0% (5 and 10% weight loss responders, respectively). In patients treated with diet alone (SB5078), reductions in $HbA_{1c}$ in the region of 0.5% have been demonstrated in weight loss responders.

From the available data it can be concluded that in responders, either 5% or 10%, sibutramine use is associated with a significant improvement in the parameters of glycaemic control ($HbA_{1c}$ and fasting blood glucose).

Total body fat and abdominal visceral fat

Patients with abdominal visceral (android) adiposity represent a subgroup of obese patients with a high risk of cardiovascular disease. Furthermore, an increase in total abdominal fat appears to be an independent predictor of coronary heart disease when the Body Mass Index (BMI) is not markedly increased. In all clinical trials with sibutramine, reductions in

waist circumference (mean change to end-point range from –4.2cm up to –11.3cm) paralleled weight loss, with dose-related reductions.

Uric acid
Elevated uric acid is well recognised to be associated with increased risk of cardiovascular morbidity and mortality. Sibutramine use is associated with a significant improvement in acid uric levels.

From the analysed data it can be concluded that sibutramine is able to induce weight loss and those associated beneficial changes in parameters that are major contributors for cardiovascular risk such as lipid profiles and glycaemic control.

**Duration of treatment**
The objective of treating obesity is to reach a clinically relevant and maintained weight loss, susceptible to decrease cardiovascular and other recognised risk factors. Such an objective can only be reached trough long-term treatment. Sibutramine has proven to be effective for 12 months. Data to support longer treatments are scant. Therefore the maximum recommended duration of treatment is one year.

**Overall conclusion on efficacy**
Sibutramine is effective in reducing body weight in long-term treatment in a certain group of patients. The rate of 10% responders, that is patients that lose 10% or more of their baseline weight, is significantly superior to what is obtained with placebo. This is particularly relevant for diabetic patients who are known to be difficult weight losers. The data available also demonstrates that sibutramine is able to promote the maintenance of weight loss for 2 years. Furthermore the secondary outcomes measures such as lipid profile, glycaemic control and total body fat are favourably influenced by the use of sibutramine in comparison with placebo. In conclusion, the therapeutic efficacy of sibutramine as an anti-obesity agent is proven according to the grounds proposed in the current guidelines, such as the CPMP Note for Guidance on Clinical Investigation of Drugs used in Weight Control (CPMP/EWP/281/96).

**SAFETY**

The overall safety profile of sibutramine containing medicinal products was reviewed. The main safety issues discussed were the cardiovascular effects and the potential for abuse and dependence.

**Cardiovascular effects**

Effects in blood pressure, heart rate and on left ventricular mass
The available data from clinical trials, clearly show that blood pressure and heart rate increase during sibutramine treatment. The increases are in average small (mean systolic blood pressure -SBP and dyastolic blood pressure - DBP increase of 2-3 mmHg and pulse rate of 4-5 bpm). However, a relevant fraction of the patients suffered clinically relevant increases (>10 mmHg), measured from baseline to endpoint, in the SBP (20.6%) or in the DBP (11.3%) and in the resting pulse (>10bpm) –25.5%. The fraction of patients who suffered clinically relevant increases (>10 mmHg) in SBP, DBP and in the resting pulse (>10bpm) at two consecutive visits was respectively 34.2%, 21.5% and 35.7%. The fractions of patients treated with placebo who experienced clinically significant increases (from baseline to endpoint and at two consecutive visits respectively) in SBP (16.1%, 28.4%), DBP (7.5%, 15.3%) and resting pulse (10.7%, 16.1%) were lower.

These findings are a cause of concern in the treatment with sibutramine as increased blood pressure is one of the best known cardiovascular risk factors and even increased heart rate is associated with increased overall mortality and cardiovascular mortality. Although there is a close positive relationship between heart rate and blood pressure, it is not known whether increased heart rate is an independent risk factor.

One of the benefits that is expected for losing weight is the reduction of blood pressure that might off-set a pre-existent hypertension or contribute for a better control of it. Moderate weight losses achieved using a variety of dietary approaches are related to blood pressure reductions of approximately 1 mmHg systolic and 2 mmHg diastolic for each 1% reduction in body-weight.

In fact the analysis of the data on sibutramine reveals that, in spite of the pharmacological tendency of sibutramine to induce increases of blood pressure and heart rate, patients really achieve a decrease of blood pressure if they manage to lose meaningful weight. In those patients who lost the most weight (≥10% of baseline weight), the changes compared to the all placebo group were not statistically significant and, with the exception of DBP in the sibutramine 10 mg group (+0.6 mmHg), were lower than the overall placebo response. This is particularly valid in patients that were, previous to enrolment, already hypertensive. In these patients sibutramine-induced weight loss was accompanied by decreases in both systolic and diastolic blood pressure compared to baseline. In those patients with the greatest weight loss (i.e. ≥10%), with the exception of DBP in the sibutramine 15 mg group (+0.3 mmHg), these changes were lower than the overall placebo response but with no statistical significant between the groups.

In addition sibutramine-induced weight loss (at 10 mg and 20 mg, the latter dosage not being at the therapeutic dosages recommended in the SPC) was associated with decreases in left ventricular mass index (LVMI). In one study (SB 104) this beneficial trend in reduction of LVMI was greater in the two sibutramine treatment groups (-4.4 ± 10.7 g/m, -4.3 ± 10.9 g/m and -3.0 ± 11.9 g/m for sibutramine 10 mg, sibutramine 20 mg and placebo, respectively). In those patients who lost the most weight (≥5% and ≥10% of their baseline weight), further reductions in LVMI were evident in all treatment groups. Thus, not only were the expected reductions in left ventricular mass index associated with weight loss, but also the reductions in LVMI were commensurate with the amount of weight loss.

Both results (on blood pressure and LVMI) demonstrate that there is a sub-set of patients exposed to sibutramine that are not only put at risk by an increase in the blood pressure and heart rate but can also have a benefit in these parameters. To identify this subset of patients the MAH proposed the two following complementary measures:

- Selection of patients that are likely to become meaningful weight losers: in those patients with an inadequate response to sibutramine 10 mg (defined as less than 2kg weight loss after 4 weeks of treatment) the dose may be increased to sibutramine 15 mg and treatment must be discontinued in patients who have responded inadequately, i.e. those who lost less than 2 kg weight after 4 weeks of treatment.
- Close monitoring of blood pressure and heart rate in the consultations in order to identify and consequently suspend the treatment in those patients that show clinical relevant increases in these parameters. The actual data show that those increases occur in the first 3 months of treatment in 60% of the patients. These figures make the monitoring option realistic.

In conclusion it can be stated that increases in blood pressure and heart rate are predictable adverse reactions, understandable on basis of the mechanism of action and likely to be manageable by prospectively implemented measures. Therefore special warnings with regard to the monitoring of these parameters have been included in the amended SPC (see Annex III of the CPMP Opinion).

Cardiovascular morbidity and mortality

- Cardiovascular and cerebrovascular events

  Effects of sibutramine on cardiovascular mortality and morbidity can only be demonstrated by an appropriate large clinical trial that, so far, is not available: neither for sibutramine nor to any other anti-obesity drug. It should be noted that the MAH proposed to perform a clinical trial to evaluate the impact of sibutramine use on cardiovascular risk, particularly from a safety perspective (see also Annex IV of the CPMP Opinion).

  At the moment the only achievable reassurance with regard to these parameters is to show that, at least, sibutramine does not induce a deleterious effect on cerebrovascular morbidity and mortality. Currently available data are data on prevalence / incidence extracted from the database assembled by the MAH during the clinical development. Analysis of this database, which has an important size (n= 8200, 1344 of which exposed to sibutramine for ≥12 months), and analysis of data from post-marketing experience (2.6 million of patients treated of whom approximately 1.3 million were in the USA) do not show any sign regarding cerebrovascular morbidity and mortality associated with sibutramine. The incidence of events is even inferior to the one expected taking in account the epidemiological data available. The data confirm, however, a higher incidence of hypertension and palpitations associated to the use of sibutramine as previously mentioned.

- Cardiac valvulopathies

  An increased risk of cardiac valvulopathies has been associated with some anti-obesity drugs, namely fenfluramines. The mechanism of this adverse reaction is not known. With regard to

sibutramine the MAH provided data of 2 echocardiographic studies that address this issue. In one study a total of 210 patients (sibutramine and placebo groups) were studied and another one included 183 patients. The prevalence of left-sided cardiac valve dysfunction using FDA case definition was 2.3% to 2.6% and similar for the two treatment groups. This issue is addressed in the SPC (see Annex III of the CPMP Opinion) in accordance to these data.

- Primary Pulmonary hypertension (PPH)
  Several anti-obesity drugs have been associated with an increased risk of PPH. With regard to sibutramine no case of unequivocal pulmonary hypertension causally related with sibutramine could be identified from post-marketing data. Furthermore the MAH provided a detailed report on the cases of dyspnoea: 21 cases of dyspnoea have been reported by health professionals. These cases show no common pattern, the clinical background being varied and the explanations for dyspnoea multiple. From these cases there is nothing that suggests that the complaint of dyspnoea was related with pulmonary hypertension.
  The issue of PPH is duly addressed in the SPC (see Annex III of the CPMP Opinion).

**Potential for drug abuse and drug dependence**

Data analysed on this respect included abuse potential studies, data from the clinical trials and data from the post-marketing experience and the potential recreational use of sibutramine. From these data it can be stated:

- Sibutramine does not possess reinforcing activity based on data from the primate self-administration model.
- Sibutramine has been evaluated for its abuse liability versus other psychostimulant drugs in two separate rodent drug-discrimination models. Both drug discrimination studies demonstrate a lack of psychostimulant abuse potential with sibutramine.
- In three studies in experienced polydrug users, sibutramine did not produce euphorigenic changes or reinforcing activity that are characteristic of drugs of abuse, like amphetamines. No evidence of psychological or physical dependence was detected in the clinical study database that includes data from over 8,200 subjects (obese or depressed patients, or healthy volunteers) exposed to sibutramine. More than 1,300 of these subjects have taken sibutramine for a period more than one year. There was no evidence of misuse/abuse or illicit diversion of sibutramine during the clinical studies. The extensive US post-marketing surveillance programme has detected no evidence abuse of sibutramine. There has not been any spontaneous post-marketing report of illicit recreational abuse of sibutramine.

*In conclusion it can be said that in spite of the fact that sibutramine is an appetite suppressant drug and, at a molecular level, has affinity for the dopamine transporter, which would raise suspicion of a potential for drug abuse, the discriminative studies in rodents did not show any tendency for such abuse potential. Furthermore a small primate study could not also show abuse potential. The data from human studies and the real life exposure is reassuring. Although it is sensible to keep monitoring for any signs of drug abuse in patients treated with sibutramine, there is no basis to consider sibutramine as a substance with potential for abuse. The MAH has committed to take measures with regard to monitoring of drug dependence and drug abuse (see also Annex IV of the CPMP Opinion).*

***Overall conclusion on safety***

Concerning safety the major problem of sibutramine is related with its own sympathomimetic effects, namely increases in blood pressure and heart rate and their long-term consequences to the cardiac function. The mean increases in blood pressure and heart rate are small (2-3 mmHg and 4-5 bpm) and are compensated by the reduction in blood pressure determined by the weight loss, mainly in the 5% and 10% responders. Furthermore these increases are predictable and can be identified by monitoring. Apart from the safety concerns above-mentioned, no other specific safety concerns were identified in the five Periodic Safety Update Reports submitted by the MAH.

From the available data there is no evidence that sibutramine is associated with drug dependence or drug abuse. Other risks associated with several anti-obesity drugs such as cardiac valvulopathies and primary pulmonary hypertension have not been associated with sibutramine. However, as a precautionary measure, these potential issues should still be monitored in the long run.

## BENEFIT/RISK ANALYSIS

Regarding efficacy sibutramine is effective in reducing body weight in long-term treatment in a certain group of patients. The rate of 10% responders, that is patients that lose 10% or more of their baseline weight, is significantly superior to what is obtained with placebo. The data available also demonstrates that sibutramine is able to promote the maintenance of weight loss for 2 years. Furthermore the secondary outcomes measures such as lipid profile, glycaemic control and total body fat are favourably influenced by the use of sibutramine in comparison with placebo. In conclusion, sibutramine has therapeutic efficacy in the treatment of obesity.

Regarding safety sibutramine increases the blood pressure and heart rate. However, the mean increases in these parameters are small (2-3 mmHg and 4-5 bpm) and are compensated by the reduction in blood pressure determined by the weight loss, mainly in the 5% and 10% responders. Furthermore these increases are predictable and can be identified by monitoring. Apart from the safety concerns above-mentioned, no other specific safety concerns were identified in the five Periodic Safety Update Reports submitted by the MAH.
From the available data there is no evidence that sibutramine is associated with drug dependence or drug abuse. Other risks associated with several anti-obesity drugs such as cardiac valvulopathies and primary pulmonary hypertension have not been associated with sibutramine. However, as a precautionary measure, these potential issues should still be monitored in the long run.

Therefore the CPMP considered that the benefit/risk balance of sibutramine containing medicinal products is favourable and the Marketing Authorisations should be maintained according to:

1. The Summaries of Product Characteristics as set out in Annex III of the CPMP Opinion with emphasis to the following:

   - Therapeutic Indications
     Sibutramine is indicated as adjunctive therapy within a weight management programme for:
     - Patients with nutritional obesity and a body mass index (BMI) of 30kg/$m^2$ or higher
     - Patients with nutritional excess weight and a BMI of 27kg/$m^2$ or higher, if other obesity related risk factors such as type 2 diabetes or dyslipidaemia are present.

   - Special Warnings
     Reinforce of warnings with regard to the monitoring of blood pressure and heart rate.

2. The CPMP requirements set out in Annex IV of the CPMP Opinion with regard to:

   - Clinical studies
     A clinical trial to evaluate the impact of sibutramine in the cardiovascular risk should be performed.
     The MAH proposed an outline of a protocol for such a study. The outline of the protocol was discussed by a CPMP Ad-Hoc Expert Group and comments were provided to the MAH. The study proposed is a randomised parallel, placebo-controlled trial with an approximated duration of 5 years to allow an enrolment period up to 2 years and a follow-up of at least 3 years. The population is selected to be at high risk for cardiovascular events. The MAH also agreed to stratify for diabetic and non-diabetic patients in order to get at least 50% of diabetic patients. The population to be enrolled (sample size will be approximately 11 000 high-risk patients) will be males or females aged 50 years and above with a documented history of failure to lose weight by diet alone, BMI≥27 kg/$m^2$, type 2 diabetes and /or hypertension plus low HDL-cholesterol. The following patients will be excluded: patients with history of recent (<1 year) coronary artery disease (angina pectoris, previous myocardial infarctions) or recent (< 1 year) cerebrovascular disease (eg stroke or TIA – transient ischaemic attack), congestive heart failure moderate/severe –(Fontaine stage III and IV), peripheral arterial occlusive disease, cardiac dysrhythmias (asymptomatic atrial or ventricular premature beats are allowed), inadequately controlled hypertension (> 160/100 mmHg). Other exclusion criteria are detailed in the outline protocol proposed by the MAH.
     The primary outcome measure will be a combined end-point of non-fatal coronary heart disease (CHD) events (including angina pectoris and myocardial infarctions), congestive heart failure, non-fatal cerebrovascular events (including haemorrhagic or ischaemic strokes, transient ischaemic attacks) and cardiovascular deaths (including sudden death).

After discussion of the outline protocol proposed by the MAH the CPMP considered that further amendments were needed. The MAH committed to include such proposed amendments in the final study protocol to be submitted within 4 months of the CPMP Opinion.

- Post-marketing data
  6-monthly Periodic Safety Update Reports should be provided to the CPMP at least for the next two years after the adoption of the CPMP Opinion.

- Monitoring of drug abuse and drug dependence
  Measures to monitor drug dependence should be put in place by the MAH.
  The MAH has already proposed to conduct different surveillance activities, namely:
  - Monitoring drug abuser populations that frequent drug abuse treatment clinics with a questionnaire in order to estimate familiarity with sibutramine in the streets and to elicit possible misuse of sibutramine.
  - Telephone surveillance of cases of overdose in order to ascertain if they occurred in prescribed users or in abusers.
  - Monitoring sales to detect signs of recreational use.
  - Monitoring Internet sites to detect recreational or abuse interest across chats.
  - Usual pharmacovigilance activities.

**GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS**

Whereas

- The Committee considered the referral made under article 12 of Council Directive 75/319/EEC as amended, for sibutramine containing medicinal products;

- The Committee agreed that sibutramine containing medicinal products are effective in reducing body weight in long-term treatment and are able to promote the maintenance of weight loss. Furthermore sibutramine is able to induce beneficial changes in the co-morbid conditions and cardiovascular risk factors associated to obesity such as lipid profile, glycaemic control and total body fat.

- The Committee agreed that there were concerns related to the safety of sibutramine containing medicinal products mainly in relation to the increase in blood pressure and heart rate. However, the mean increases are small and are considered to be manageable by a regular monitoring of these parameters.

- The Committee considered the benefit/risk balance of sibutramine containing medicinal products to be favourable as adjunctive therapy within a weight management programme, for patients with nutritional obesity and a body mass index of 30kg/$m^2$ or higher or in patients with nutritional excess weight and a BMI of 27kg/$m^2$ or higher, if other obesity related risk factors such as type 2 diabetes or dyslipidaemia are present, and, therefore, concluded that the Marketing Authorisations for these medicinal products should be maintained as amended in accordance with the Summary of Product Characteristics set out in Annex III and under the conditions set out in Annex IV.

As a consequence the CPMP has recommended the maintenance of the Marketing Authorisations for sibutramine containing medicinal products (see Annex I) as amended in accordance with the Summary of Product Characteristics set out in Annex III and under the conditions set out in Annex IV.

**ANNEX III**
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

<Tradename>

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule of <tradename> 10 mg contains 10 mg of sibutramine hydrochloride monohydrate (equivalent to 8.37 mg of sibutramine).

One capsule of <tradename> 15mg contains 15mg of sibutramine hydrochloride monohydrate (equivalent to 12.55 mg of sibutramine).

*For excipients, see 6.1*

## 3. PHARMACEUTICAL FORM

*10 mg* Hard capsule with a blue cap and yellow body

*15 mg* Hard capsule with a blue cap and a white body

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

<Tradename> 10 mg / 15mg is indicated as adjunctive therapy within a weight management programme for:

- Patients with nutritional obesity and a body mass index (BMI) of 30 $kg/m^2$ or higher
- Patients with nutritional excess weight and a BMI of 27 $kg/m^2$ or higher, if other obesity-related risk factors such as type 2 diabetes or dyslipidaemia are present.

Note:

<Tradename> may only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone, i.e. patients who have difficulty achieving or maintaining >5% weight loss within 3 months.

Treatment with <Tradename> 10 mg / 15mg should only be given as part of a long-term integrated therapeutic approach for weight reduction under the care of a physician experienced in the treatment of obesity. An appropriate approach to obesity management should include dietary and behavioural modification as well as increased physical activity. This integrated approach is essential for a lasting change in eating habits and behaviour which is fundamental to the long-term maintenance of the reduced weight level once <Tradename> is stopped. Patients should change their lifestyle while on <Tradename> so that they are able to maintain their weight once drug treatment has ceased. They should be informed that, if they fail to do so, they may regain weight. Even after cessation of <Tradename> continued monitoring of the patient by the physician should be encouraged.

### 4.2 Posology and method of administration

**Adults**: The initial dose is 1 capsule of <Tradename> 10 mg swallowed whole, once daily, in the morning, with liquid (eg a glass of water). The capsule can be taken with or without food.

In those patients with an inadequate response to <Tradename> 10 mg (defined as less than 2 kg weight loss after 4 weeks treatment), the dose may be increased to 1 capsule of <Tradename> 15 mg once daily, provided that <Tradename> 10 mg was well tolerated.

Treatment must be discontinued in patients who have responded inadequately to <Tradename> 15 mg (defined as less than 2 kg weight loss after 4 weeks treatment). Non-responders are at a higher risk of undesirable effects (see section 4.8 “Undesirable Effects”).

**Duration of treatment**: Treatment must be discontinued in patients who have not responded adequately, i.e. whose weight loss stabilises at less than 5% of their initial bodyweight or whose weight loss within 3 months after starting therapy has been less than 5% of their initial bodyweight. Treatment should not be continued in patients who regain 3 kg or more after previously achieved weight loss.

In patients with associated co-morbid conditions, it is recommended that treatment with <Tradename> 10mg / 15mg should only be continued if it can be shown that the weight loss induced is associated with other clinical benefits, such as improvements in lipid profile in patients with dyslipidaemia or glycaemic control of type 2 diabetes.

<Tradename> 10 mg / 15mg should only be given for periods up to one year. Data on use over one year is limited.

**4.3 Contraindications**

- Known hypersensitivity to sibutramine hydrochloride monohydrate or any other component of the product
- Organic causes of obesity
- History of major eating disorders.
- Psychiatric illness. Sibutramine has shown potential antidepressant activity in animal studies and, therefore it cannot be excluded that sibutramine could induce a manic episode in bipolar patients.
- Gilles de la Tourette's syndrome
- Concomitant use, or use during the past two weeks, of monoamine oxidase inhibitors or of other centrally-acting drugs for the treatment of psychiatric disorders (such as antidepressants, antipsychotics) or for weight reduction, or tryptophan for sleep disturbances.
- History of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or TIA)
- Inadequately controlled hypertension (>145/90 mmHg) ( see section 4.4 “Special warnings and special precautions”)
- Hyperthyroidism
- Severe hepatic impairment
- Severe renal impairment
- Benign prostatic hyperplasia with urinary retention
- Phaeochromocytoma
- Narrow angle glaucoma
- History of drug, medication or alcohol abuse
- Pregnancy and lactation (see section 4.6 “Pregnancy and lactation”)
- Children and young adults up to the age of 18 years, owing to insufficient data
- Patients above 65 years of age, owing to insufficient data.

**4.4 Special warnings and special precautions for use**

Warnings:

Blood pressure and pulse rate should be monitored in all patients on <Tradename> 10 mg / 15mg, as sibutramine has caused clinically relevant increases in blood pressure in some patients. In the first three months of treatment, these parameters should be checked every 2 weeks; between month 4 and 6 these parameters should be checked once monthly and regularly thereafter, at maximum intervals of three months. Treatment should be discontinued in patients who have an increase, at two consecutive visits, in resting heart rate of ≥10 bpm or systolic/diastolic blood pressure of ≥10 mmHg. In previously well-controlled hypertensive patients, if blood pressure exceeds 145/90 mmHg at two consecutive readings, treatment should be discontinued (see section 4.8 "Undesirable effects, cardiovascular changes"). In patients with sleep apnoea syndrome particular care should be taken in monitoring blood pressure.

Although sibutramine has not been associated with primary pulmonary hypertension, it is important, in view of general concerns with anti-obesity drugs, to be on the look out for symptoms such as progressive dyspnoea, chest pain and ankle oedema in the course of routine check-ups. The patient should be advised to consult a doctor immediately if these symptoms occur.

<Tradename> 10 mg / 15mg should be given with caution to patients with epilepsy.

Increased plasma levels have been observed in the assessment of sibutramine in patients with mild to moderate hepatic impairment. Although no adverse effects have been reported, <Tradename> 10 mg / 15mg should be used with caution in these patients.

Although only inactive metabolites are excreted by the renal route, <Tradename> 10 mg /15mg should be used with caution in patients with mild to moderate renal impairment.

<Tradename> 10 mg / 15mg should be given with caution to patients who have a family history of motor or verbal tics.

Women of child-bearing potential should employ adequate contraception whilst taking <Tradename> 10 mg / 15mg.

There is the possibility of drug abuse with CNS-active drugs. However, available clinical data have shown no evidence of drug abuse with sibutramine.

There are general concerns that certain anti-obesity drugs are associated with an increased risk of cardiac valvulopathy. However, clinical data show no evidence of an increased incidence with sibutramine.

Patients with a history of major eating disorders such as anorexia nervosa and bulimia nervosa are contraindicated. No data are available for sibutramine in the treatment of patients with Binge (compulsive) Eating Disorder.

**4.5 Interactions with other medicaments and other forms of interaction**

Sibutramine and its active metabolites are eliminated by hepatic metabolism; the main enzyme involved is CYP3A4, and CYP2C9 and CYP1A2 can also contribute. Caution should be exercised on concomitant administration of <Tradename> 10 mg / 15mg with drugs which affect CYP3A4 enzyme activity (see section 5.2 "Pharmacokinetic properties"). CYP3A4 inhibitors include ketoconazole, itraconazole, erythromycin, clarithromycin, troleandomycin and cyclosporin. Co-administration of ketoconazole or erythromycin with sibutramine increased plasma concentrations (AUC) of sibutramine active metabolites (23% or 10% respectively) in an interaction study. Mean heart rate increased by up to 2.5 beats per minute more than on sibutramine alone.
Rifampicin, phenytoin, carbamazepine, phenobarbital and dexamethasone are CYP3A4 enzyme inducers and may accelerate sibutramine metabolism, although this has not been studied experimentally.

The simultaneous use of several drugs, each of which increases levels of serotonin in the brain, may give rise to serious interactions. This phenomenon is called serotonin syndrome and may occur in rare cases in connection with the simultaneous use of a selective serotonin reuptake inhibitor [SSRI] together with certain antimigraine

drugs (such as sumatriptan, dihydroergotamine), or along with certain opioids (such as pentazocine, pethidine, fentanyl, dextromethorphan), or in the case of simultaneous use of two SSRIs.

As sibutramine inhibits serotonin reuptake (among other effects), <Tradename> 10 mg / 15mg should not be used concomitantly with other drugs which also raise serotonin levels in the brain.

Concomitant use of <Tradename> 10 mg / 15mg with other drugs which may raise the blood pressure or heart rate has not been systematically evaluated. Drugs of this type include certain cough, cold and allergy medications (eg ephedrine, pseudoephedrine), and certain decongestants (eg xylometazoline). Caution should be used when prescribing <Tradename> 10 mg / 15mg to patients who use these medicines.

<Tradename> 10 mg / 15mg does not impair the efficacy of oral contraceptives.

At single doses, there was no additional impairment of cognitive or psychomotor performance when sibutramine was administered concomitantly with alcohol. However, the consumption of alcohol is not compatible with the recommended dietary measures as a general rule.

No data on the concomitant use of <Tradename> 10 mg / 15mg with orlistat are available.

Two weeks should elapse between stopping sibutramine and starting monoamine oxidase inhibitors.

**4.6 Pregnancy and lactation**

**Use in pregnancy:** Sibutramine should not be used during pregnancy. It is generally considered inappropriate for weight-reducing drugs to be used during pregnancy, so women of childbearing potential should employ an adequate method of contraception while taking sibutramine and notify their physician if they become pregnant or intend to become pregnant during therapy. No controlled studies with <Tradename> have been conducted in pregnant women. Studies in pregnant rabbits have shown effects on reproduction at maternally toxic doses (see section 5.3 “Preclinical safety data”). The relevance of these findings to humans is unknown.

**Use in lactation:** It is not known whether sibutramine is excreted in human breast milk and therefore administration of <Tradename> 10 mg / 15mg is contraindicated during lactation.

**4.7 Effects on ability to drive and use machines**

Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any centrally-acting drug may impair judgement, thinking or motor skills. Therefore, patients should be cautioned that their ability to drive a vehicle, operate machinery or work in a hazardous environment may be impaired when taking <Tradename> 10 mg / 15mg.

**4.8 Undesirable effects**

Most side effects occurred at the start of treatment (during the first 4 weeks). Their severity and frequency diminished over time. They were generally not serious, did not entail discontinuation of treatment, and were reversible.

The side effects observed in clinical trials are listed below by body system (very frequent >10%, frequent 1-10%):

| Body system | Incidence | Undesirable effects |
|---|---|---|
| Cardiovascular system<br>(see "cardiovascular changes") | Frequent | Tachycardia<br>Palpitations<br>Raised blood pressure/hypertension<br>Vasodilation (hot flush) |
| Gastrointestinal system | Very frequent | Loss of appetite<br>Constipation |
| | Frequent | Nausea<br>Haemorrhoid aggravation |
| Central nervous system | Very frequent | Dry mouth<br>Insomnia |
| | Frequent | Light-headedness<br>Paraesthesia<br>Headache<br>Anxiety |
| Skin | Frequent | Sweating |
| Sensory functions | Frequent | Taste, perversion |

The following clinically significant adverse events occurred in individual cases under treatment with sibutramine:

- Acute interstitial nephritis
- Mesangiocapillary glomerulonephritis
- Henoch-Schönlein purpura
- Seizures
- Thrombocytopenia
- Reversible increases in liver enzyme
- Acute psychotic attack after treatment in one patient with schizo-affective disorder which presumably existed prior to treatment

Withdrawal symptoms such as headache and increased appetite have rarely been observed. There is no evidence of a withdrawal or abstinence syndrome or mood swings on cessation of treatment.

Rare cases of blurred vision have been reported from post-marketing surveillance.

Cardiovascular changes

A mean increase in resting systolic and diastolic blood pressure of 2 - 3 mmHg, and a mean increase in heart rate of 3 - 7 beats per minute have been observed.

Higher increases in blood pressure and heart rate cannot be excluded in isolated cases.

Any clinically significant increase in blood pressure and pulse rate tends to occur early on in treatment (first 4 - 12 weeks). Therapy should be discontinued in such cases (see section 4.4 "Special warnings and precautions for use")/.

For use of <Tradename> 10 mg / 15mg in patients with hypertension, see sections 4.3 "Contraindications" and 4.4 "Special warnings and special precautions".

**4.9 Overdose**

There is limited experience of overdosing with sibutramine. No specific therapeutic measures are recommended and there is no specific antidote. Treatment should consist of the general measures employed in the management of overdosing, such as keeping airways unobstructed, monitoring of cardiovascular functions and general symptomatic and supportive measures. Early administration of activated charcoal may delay the absorption of

sibutramine. Gastric lavage may also be of benefit. Cautious use of beta-blockers may be indicated in patients with elevated blood pressure or tachycardia.

There are a number of reports of overdose in humans (including accidental ingestion by children as young as 18 months) where doses of up to 500 mg sibutramine hydrochloride monohydrate were ingested. A heart rate of 160 beats per minute was observed in one patient who took 500 mg sibutramine hydrochloride monohydrate. Except in one case of multiple drug intoxication with alcohol (where the patient died, possibly due to inhalation of vomit), there were no complications and the individuals made a full recovery.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-obesity drug, ATC code A08A A10.

Sibutramine produces its therapeutic effects predominantly via its active secondary and primary amine metabolites (metabolite 1 and metabolite 2) which are inhibitors of noradrenaline, serotonin (5-hydroxytryptamine; 5-HT) and dopamine reuptake. In human brain tissue, metabolite 1 and metabolite 2 are ~3-fold more potent as in vitro inhibitors of noradrenaline and serotonin reuptake than of dopamine reuptake. Plasma samples taken from sibutramine-treated volunteers caused significant inhibition of both noradrenaline reuptake (73%) and serotonin reuptake (54%) with no significant inhibition of dopamine reuptake (16%). Sibutramine and its metabolites are neither monoamine-releasing agents nor are they monoamine oxidase inhibitors. They have no affinity with a large number of neurotransmitter receptors, including serotonergic (5-HT1, 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C), adrenergic (β1, β2, β3, α1, α2), dopaminergic (D1-like, D2-like), muscarinic, histaminergic (H1), benzodiazepine and NMDA receptors.

In animal models using lean growing and obese rats, sibutramine produces a reduction in bodyweight gain. This is believed to result from its impact on food intake, i.e. by enhancing satiety, but enhanced thermogenesis also contributes to weight loss. These effects have been shown to be mediated by the inhibition of serotonin and noradrenaline re-uptake.

In clinical trials in man, <Tradename> was shown to effect weight loss by enhancing satiety. Data are also available which demonstrate a thermogenic effect of <Tradename> by attenuating the adaptive decline in resting metabolic rate during weight loss. Weight loss induced by <Tradename> is accompanied by beneficial changes in serum lipids and glycaemic control in patients with dyslipidaemia and type 2 diabetes, respectively.

In obese patients with type 2 diabetes mellitus weight loss with sibutramine was associated with mean reductions of 0.6% (unit) in HbA1c. Similarly, in obese patients with dyslipidaemia, weight loss was associated with increases in HDL-cholesterol of 12-22% and reductions in triglycerides of 9 – 21%.

### 5.2 Pharmacokinetic properties

Sibutramine is well absorbed and undergoes extensive first-pass metabolism. Peak plasma levels ($T_{max}$) were achieved 1.2 hours after a single oral dose of 20 mg of sibutramine hydrochloride monohydrate. The half-life of the parent compound is 1.1 hours. The pharmacologically active metabolites 1 and 2 reach $T_{max}$ in three hours with elimination half-lives of 14 and 16 hours, respectively. Linear kinetics have been demonstrated over the dose range of 10 to 30 mg, with no dose-related change in the elimination half-lives but a dose-proportionate increase in plasma concentrations. On repeated dosing, steady-state concentrations of metabolites 1 and 2 are achieved within 4 days, with an approximately 2-fold accumulation. The pharmacokinetics of sibutramine and its metabolites in obese subjects are similar to those in normal weight subjects. The relatively limited data available so far provide no evidence of a clinically relevant difference in the pharmacokinetics of males and females. The pharmacokinetic profile observed in elderly healthy subjects (mean age 70 years) was similar to that seen in young healthy subjects. In subjects with moderate hepatic impairment, bioavailability of the active metabolites was 24% higher after a single dose of sibutramine. Plasma protein binding of sibutramine and its metabolites 1 and 2 amounts to approximately 97%, 94% and 94%, respectively. Hepatic metabolism is the major route of elimination of sibutramine and its active metabolites 1 and 2. Other (inactive) metabolites are excreted primarily via the urine, at a urine: faeces ratio of 10 : 1.

*In vitro* hepatic microsome studies indicated that CYP3A4 is the major cytochrome P450 isoenzyme responsible for sibutramine metabolism. *In vitro,* there was no indication of an affinity with CYP2D6, a low capacity enzyme involved in pharmacokinetic interactions with various drugs. Further *in vitro* studies have revealed that sibutramine has no significant effect on the activity of the major P450 isoenzymes, including CYP3A4. The

CYP450s involved in the further metabolism of metabolite 2 were shown (*in vitro*) to be CYP3A4 and CYP2C9. Although there are no data at present, it is likely that CYP3A4 is also involved in further metabolism of metabolite 1.

### 5.3 Preclinical safety data

The toxicity of sibutramine seen after single doses in experimental animals has generally been a result of exaggerated pharmacodynamic effects. Longer-term treatment was associated with only mild pathological changes and secondary or species-related findings. It follows that they are unlikely to present concerns during the proper clinical use of sibutramine. Reproduction studies were conducted in rats and rabbits. In rabbits, one study showed a slightly higher incidence of fetal cardiovascular anomalies in the treatment groups than in the control group, while another study showed a lower incidence than in controls. In addition, in the latter study but not in the former, the treatment group had slightly more fetuses with two minor anomalies (a tiny thread-like ossified connection between the maxilla and jugal bones, and very slight differences in the spacing of the roots of some small arteries from the aortic arch). The relevance of these findings to humans is unknown. Sibutramine's use in human pregnancy has not been investigated. Extensive genetic toxicity tests disclosed no evidence of sibutramine-induced mutagenicity. Studies in rodents have shown that sibutramine has no carcinogenic potential relevant to man.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content: lactose monohydrate, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica.

Capsule shell *(10 mg):* indigo carmine (E 132), titanium dioxide (E 171), gelatin, sodium lauryl sulphate, quinoline yellow (E 104)

Capsule shell *(15 mg):* indigo carmine (E 132), titanium dioxide (E 171), gelatin, sodium lauryl sulphate

Printing ink: dimethicone, iron oxides and hydroxides (E 172), shellac, soybean lecithin (E 322), titanium dioxide (E 171).

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf-life

3 years

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package, keep blister pack in the outer carton

### 6.5 Nature and contents of container

<Tradename> 10 mg / 15 mg, capsules in a PVC/PVDC blister strip pack.
Calendar pack containing 28 capsules (4 weeks)
Calendar pack containing 56 capsules (8 weeks)
Calendar pack containing 98 capsules (14 weeks)
Hospital pack (calendar pack) containing 28 capsules
Hospital pack (calendar pack) containing 280 (10 x 28) capsules

### 6.6 Instructions for use / handling

None

## 7. MARKETING AUTHORISATION HOLDER

Knoll Deutschland GmbH
Postfach 210660
67006 Ludwigshafen
Germany
Rathausplatz 10 - 12
67059 Ludwigshafen
Germany

Phone: (0621) 5940
Telefax: (0621) 5 94 17 71

## 8. MARKETING AUTHORISATION NUMBER

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

November 2000

**ANNEX IV**
**CONDITIONS OF THE MARKETING AUTHORISATIONS**

# Conditions of the Marketing Authorisations

## CPMP requirements in relation to clinical studies and post-marketing data

### Clinical studies

A clinical study to evaluate the impact of sibutramine in the cardiovascular risk, particularly from a safety perspective, should be performed.

A final study protocol should be submitted for review within four months of the CPMP opinion and 6-monthly updates on the progress of the study (safety and recruitment / drop-out rates) should be provided. Interim results of such study should be provided at least two years after its start.

### Post-marketing data

Six-monthly Periodic Safety Update Reports should be provided for review by the CPMP at least for the next two years after the adoption of the CPMP Opinion.

### Monitoring of drug abuse and drug dependence

Measures to monitor drug abuse and drug dependence should be put in place by the MAH. The MAH should provide a plan to clarify its strategy to fulfil this commitment. The data gathered from this monitoring should be provided for review at 6-month intervals.