The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

2 December 2002
CPMP/4514/02/Final

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS OPINION FOLLOWING AN ARTICLE 31 REFERRAL

SIBUTRAMINE

International Nonproprietary Name (INN): **Sibutramine**

BACKGROUND INFORMATION

Sibutramine is an anti-obesity agent, which inhibits the reuptake of norepinephrine and serotonin.

On 4 October 1999, sibutramine containing medicinal products were subjected to a referral under Article 12 of Council Directive 75/319/EEC, as amended triggered by Belgium, who 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. Belgium requested the CPMP to reassess the benefit/risk of sibutramine containing medicinal products.

Subsequently, the CPMP reviewed the safety and efficacy of sibutramine containing medicinal products and after considering the commitment from the Marketing Authorisation Holder, adopted an opinion on 16 November 2000, recommending the maintenance of the Marketing Authorisations for sibutramine containing medicinal products in accordance with an amended Summary of Product Characteristics (SPC) and under certain conditions, such as the performance of a clinical study to evaluate the impact of sibutramine on the cardiovascular risk and the submission of six-monthly Periodic Safety Update Reports (PSURs) for review by the CPMP. On the basis of the Opinion adopted by the CPMP, the European Commission issued a decision on 26 March 2001.

On 6 March 2002 the Italian Authorities circulated a Rapid Alert to all MS, EMEA and EC, informing all parties of their decision to temporarily suspend the Marketing Authorisations for sibutramine containing medicinal products in Italy. This suspension was mainly due to safety concerns, based on a number of reports of serious adverse reactions associated with sibutramine in Italian patients, including two fatal cases. Subsequently, Italy triggered on 19 March 2002 a referral to the EMEA, under Article 31 of Directive 2001/83/EC (formerly Article 12 of Council Directive 75/319/EEC, as amended), requesting the CPMP to give an opinion on whether the marketing authorisations for sibutramine containing medicinal products, in the current approved therapeutic indications, should be maintained, changed, suspended or withdrawn, on the basis of reported serious adverse reactions associated with these medicinal products. Italy considered that for public health protection, a reassessment of the efficacy and safety of sibutramine containing medicinal products was necessary.

The referral procedure started on 21 March 2002. Written explanations were provided by the Marketing Authorisation Holders (MAHs) on 12 April and 5 June 2002.

On the basis of the available data on sibutramine, the CPMP considered that the benefit/risk balance of sibutramine containing medicinal products is favourable, and therefore adopted on 27 June 2002, an Opinion recommending the maintenance of the Marketing Authorisations for sibutramine containing medicinal products referred in Annexes IA and IB of the Opinion, as amended in accordance with the SPC set out in Annex III and under the conditions set out in Annex IV of the Opinion.

A summary of the scientific conclusions is provided in the Annex II.

The final opinion was converted into a Decision by the European Commission on 15 October 2002.

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ANNEX I

LIST OF THE INVENTED NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDERS, STRENGTHS, PHARMACEUTICAL FORMS, ROUTE OF ADMINISTRATION, PACKAGING AND PACKAGE SIZES

SIBUTRAMINE CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
AUSTRIA	Abbott Ges.m.b.H. Diefenbachgasse 35 A-1150 Wien	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 28 (clinic) 280 (10x28)
AUSTRIA	Abbott Ges.m.b.H. Diefenbachgasse 35 A-1150 Wien	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 28 (clinic) 280 (10x28)
AUSTRIA	Abbott Ges.m.b.H. Diefenbachgasse 35 A-1150 Wien	Meridia	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 28 (clinic) 280 (10x28)
AUSTRIA	Abbott Ges.m.b.H. Diefenbachgasse 35 A-1150 Wien	Meridia	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 28 (clinic) 280 (10x28)

BELGIUM	Abbott S.A. Parc Scientifique 2 rue du Bosquet B-1348 Ottignes – L.L.N. Belgium	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280
BELGIUM	Abbott S.A. Parc Scientifique 2 rue du Bosquet B-1348 Ottignes – L.L.N. Belgium	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280
DENMARK	Abbott Scandinavia AB PO Box 509 16929 Solna Sweden	Reductil	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280
DENMARK	Abbott Scandinavia AB PO Box 509 16929 Solna Sweden	Reductil	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280

FINLAND	Abbott Scandinavia AB P.O.Box 509 16929 Solna Sweden	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280
FINLAND	Abbott Scandinavia AB P.O.Box 509 16929 Solna Sweden	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280
FRANCE	Knoll France 49 Avenue Georges Pompidou 92200 Levallois	Sibutral	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280
FRANCE	Knoll France 49 Avenue Georges Pompidou 92200 Levallois	Sibutral	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 Hospital pack: 28 280

GERMANY	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden	Reductil	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)
GERMANY	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden	Reductil	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)
GERMANY	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden	Reduxade	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)

GERMANY	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden	Reduxade	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)
GERMANY	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden	Zelium	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)
GERMANY	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden	Zelium	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)

GREECE	Abbott Laboratories Hellas S.A 512 Vouliagmenis Ave 174 56 Alimos - Athens Greece	Reductil	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 280
GREECE	Abbott Laboratories Hellas S.A 512 Vouliagmenis Ave, 174 56 Alimos - Athens Greece	Reductil	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 280
IRELAND	Abbott Laboratories Ireland 1 Broomhill Business Park Tallaght Dublin 24	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)
IRELAND	Abbott Laboratories Ireland 1 Broomhill Business Park Tallaght Dublin 24	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack (calendar pack): 28 280 (10 x 28)

ITALY	Knoll Deutschland GmbH Rathausplatz 10-12 67059 Ludwigshafen Germany	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280
ITALY	Knoll Deutschland GmbH Rathausplatz 10-12 67059 Ludwigshafen Germany	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280
ITALY	Bracco S.p.A. Via E. Folli, 50 20134 Milano Italy	Ectiva	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280
ITALY	Bracco S.p.A. 20134 Via E. Folli, 50 Milano Italy	Ectiva	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280
ITALY	Abbott Spa Via Pontina km. 52 04010 Campoverde di Aprilia, LT – Italy	Reduxade	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280
ITALY	Abbott SpA Via Pontina km. 52 04010 Campoverde di Aprilla, LT – Italy	Reduxade	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280

LUXEMBOURG	Abbott S.A. Parc Scientifique 2, rue du Bosquet B-1348 Ottignies – L.L.N	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280
LUXEMBOURG	Abbott S.A. Parc Scientifique 2, rue du Bosquet B-1348 Ottignies – L.L.N	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 56 98 280
NETHERLANDS	Abbott B.V. PO Box 727 NL-2130 AS Hoofddorp The Netherlands	Reductil	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 (2 x 14)
NETHERLANDS	Abbott B.V. PO Box 727 NL-2130 AS Hoofddorp The Netherlands	Reductil	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 (2 x 14)
PORTUGAL	Abbott Laboratórios, Lda Rua Cidade de Còrdova, 1-A Alfragide, 2720-100 Amadora	Reductil	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 hospital pack 28 280

PORTUGAL	Abbott Laboratórios, Lda Rua Cidade de Còrdova, 1-A Alfragide, 2720-100 Amadora	Reductil	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 hospital pack 28 280
PORTUGAL	Abbott Laboratórios, Lda Rua Cidade de Còrdova, 1-A Alfragide, 2720-100 Amadora	Zelium	15 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 hospital pack 28 280
PORTUGAL	Abbott Laboratórios, Lda Rua Cidade de Còrdova, 1-A Alfragide, 2720-100 Amadora	Zelium	10 mg	Capsule, hard	Oral use	Blister (PVC/PDVC)	28 56 98 hospital pack 28 280
SPAIN	Abbott Laboratories, S.A. Josefa Valcarcel, 48- 28027 Madrid Spain	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28
SPAIN	Abbott Laboratories, S.A. Josefa Valcarcel, 48 28027 – Madrid Spain	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28

SWEDEN	Abbott Scandinavia AB P.O.Box 509 16929 Solna, Sweden	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack: 28 280
SWEDEN	Abbott Scandinavia AB P.O.Box 509 16929 Solna, Sweden	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	Calendar pack: 28 56 98 Hospital pack: 28 280
UK	Abbott Laboratories Limited Queenborough Kent ME11 5EL	Reductil	10 mg	Capsule, Hard	Oral Use	Blister	28 30 56 60 90 98 120 280
UK	Abbott Laboratories Limited Queenborough Kent ME11 5EL	Reductil	15 mg	Capsule, Hard	Oral Use	Blister	28 30 56 60 90 98 120 280

ANNEX

LIST OF THE INVENTED NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDERS, STRENGTHS, PHARMACEUTICAL FORMS, ROUTE OF ADMINISTRATION, PACKAGING AND PACKAGE SIZES IN ICELAND

SIBUTRAMINE CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN ICELAND

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
ICELAND	Abbott Scandinavia Ab P.O.Box 509 16929 Solna, Sweden	Reductil	10 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 98
ICELAND	Abbott Scandinavia Ab P.O.Box 509 16929 Solna, Sweden	Reductil	15 mg	Capsule	Oral use	Blister (PVC/PDVC)	28 98

ANNEX II

SUMMARY OF SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND GROUNDS FOR THE CONDITIONS TO THE MARKETING AUTHORISATIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SIBUTRAMINE CONTAINING MEDICINAL PRODUCTS

Sibutramine is an anti-obesity agent which inhibits the reuptake of norepinephrine and serotonine. It was first approved in Mexico in November 1997. In the European Union (EU) it was approved in Germany in January 1999 and subsequently applications were submitted in all Member States, except France, through the Mutual Recognition Procedure (MRP). In France sibutramine containing medicinal products were authorised through a national procedure.

On 19 March 2002 Italy triggered a referral to the EMEA, under Article 31 of Directive 2001/83/EC (formerly Article 12 of Council Directive 75/319/EEC, as amended), requesting the CPMP to give an opinion on whether the marketing authorisations for sibutramine containing medicinal products, in the currently approved therapeutic indications, should be maintained or changed, suspended or withdrawn, on the basis of reported serious adverse reactions associated with these medicinal products. Italy considered that for public health protection, a reassessment of the efficacy and safety of sibutramine containing medicinal products was necessary.

On 21 March 2002, the CPMP asked the MAH to provide updated data on efficacy since the previous CPMP referral under Article 12 of Directive 75/319/EEC. The MAH was also asked to provide cumulative reviews of cardiovascular, psychiatric, electrolyte disturbances and serotonin syndrome events.

At the meeting of 25-27 June 2002 the CPMP considered the data presented by the MAH, and reached the following conclusions, based on the Joint Assessment Report prepared by the Rapporteur and Co-rapporteur.

EFFICACY

A discussion on the efficacy of sibutramine containing medicinal products took place at CPMP based on the Rapporteur/Co-Rapporteur's Assessment Report and the data presented by the MAHs. It should be noted that the CPMP requested the MAHs to only provide any new data available with respect to efficacy of sibutramine containing medicinal products since the previous referral under article 12 of Council Directive 75/319/EEC, as amended.

As answer to the CPMP question on efficacy the MAH presented the results of four new company-sponsored clinical trials as well as a review of the published literature.

In total 12518 overweight or obese patients (Body Mass Index – BMI $\geq$ 30Kg/m^2 or BMI $\geq$ 27Kg/m^2 in presence of obesity co-morbidities) were included in these studies; 1493 of them were treated in a randomised double-blind placebo- or reference-controlled setting. The treatment duration varied from 12 weeks to 72 weeks.

Weight loss

Further to the assessment of these studies the CPMP concluded that regarding the primary efficacy criterion (**weight loss**), the results did not differ from those already mentioned within the previous Article 12 procedure.

In the current reassessment of the efficacy of sibutramine containing medicinal products the CPMP confirmed that in long-term clinical trials sibutramine is effective in reducing body weight in a specific group of patients considering a low calorie diet and behavioural education as accompanying treatments.

Clinical consequences after long-term weight loss

The potential clinical consequences of intentional weight loss include 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 was considered by CPMP.

Favourable improvements of the lipid profile and the glycaemic control with the use of sibutramine can be shown. On the basis of the submitted data the CPMP concluded that in general, the findings do not differ from results already known and assessed in its Opinion of the previous Article 12 procedure.

Overall conclusion on efficacy

In conclusion, all new studies assessed by CPMP do not show any change of the overall benefit of sibutramine containing medicinal products since the assessment performed by CPMP in November 2000 (previous Article 12 procedure). As demonstrated by body weight loss or decrease of BMI, sibutramine induces a relevant decrease of body weight in the context of low calorie diet and behaviour training programs. In addition, the available data also demonstrates that the use of sibutramine is associated with improvements in secondary outcome measures such as lipid profile and glycaemic control. On the basis of the available data the CPMP concluded that sibutramine is effective in the treatment of obesity.

SAFETY

The overall safety profile of sibutramine containing medicinal products was reviewed by the CPMP. The main safety issues discussed were the cardiovascular effects, psychiatric effects, electrolyte imbalance and serotonin syndrome. Furthermore, the CPMP assessed all fatal cases associated with the use of sibutramine. The conclusions from the CPMP are hereafter presented.

Cardiovascular effects

In the framework of the current Article 31 referral, the potential of sibutramine to increase blood pressure and heart rate, as well as the increased risk of cardiac valvulopathies and primary pulmonary hypertension associated with other anti-obesity drugs, has raised concerns regarding the cardiovascular risks associated with the use of sibutramine. The MAH provided a safety reassessment of the cardiovascular risk, based on the analysis of the MAHs' clinical database. In addition the MAHs' global post-marketing surveillance database was searched for medically confirmed reports of cardiovascular events. The analysis of the MAHs' clinical database encompassed 6551 subjects who received sibutramine in the context of clinical or observational studies. In addition the MAHs' global post-marketing surveillance database was searched for medically confirmed reports of cardiovascular events received during the period 12 November 1997 to 28 February 2002.

The number and quality of cardiovascular adverse drug reactions (ADRs) associated with the use of sibutramine, taking into account the large number of subjects (> 8 million) already treated, do not raise new concerns regarding the cardiovascular risk of sibutramine. In conclusion, on the basis of the available data, no changes to the currently approved SPC with regards to cardiovascular risk are considered necessary.

However, the MAHs should continue to closely monitor cardiovascular adverse drug reactions associated with the use of sibutramine. Furthermore, it is considered of major importance that the cardiovascular outcome study (SCOUT) previously requested by CPMP should be urgently started.

Psychiatric effects

As answer to the CPMP List of Questions, the MAHs provided a detailed cumulative analysis of psychiatric events associated with the use of sibutramine covering the period from 12 November 1997 to 28 February 2002.

Despite the overall ability of antidepressants to relieve depression and to reduce the risk of suicide in depressed patients it is currently a matter of discussion if these agents also have a potential to increase

suicide ideation and behaviour in individual patients. This effect could also potentially apply to sibutramine which shares major pharmacodynamic features with some tricyclic antidepressants and antidepressants of the serotonin noradrenaline reuptake inhibitor (SNRI)-type. In the data from the MAHs a number of cases describing the occurrence of suicide ideation coincident with the start of sibutramine therapy were included. On the basis of the available data the CPMP concluded that cases of depression have been reported in patients on sibutramine. Furthermore, suicide has been reported coincident with sibutramine in a small and unpredictable subpopulation of patients. Therefore, the SPC for sibutramine containing medicinal products should be amended as follows:

Section 4.4 – Special Warnings and special precautions for use
"Cases of depression, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. Special attention is therefore required in patients with a history of depression. If signs or symptoms of depression occur during the treatment with sibutramine, the discontinuation of sibutramine and commencement of an appropriate treatment should be considered."

Section 4.8 – Undesirable effects
"Psychiatric disorders:
Depression in patients both with and without a prior history of depression (see section 4.4)."

Electrolyte imbalance
Based on the available data the CPMP concluded that there is no role for sibutramine in the development of electrolyte disorders.

Serotonin syndrome
In response to the CPMP List of Questions, the MAHs provided an overall analysis of the risk associated with sibutramine therapy to cause a serotonin syndrome. The analysis covered the period from 12 November 1997 to 28 February 2002.
The available data show that the number of cases associated with sibutramine use, which eventually indicate a serotonin syndrome, is relatively small and all of them were non-fatal cases. Furthermore, all reports of serotonin syndrome coincident with sibutramine occurred in patients taking other serotonergic agents. In addition, the current approved SPC for sibutramine containing medicinal products already includes appropriate wording in order to prevent a combined use of sibutramine with other serotonergics. Taking this into account the CPMP concluded, that no further amendments of the SPC or other regulatory measures are required regarding the serotonin-syndrome.

Fatal events
An update of all fatal events associated with the use of sibutramine was presented by the MAHs.
Analysis of all individual fatal cases demonstrates the following:
- There is substantial heterogeneity in the causes of death.
- In most cases, alternative etiologies and complicating conditions, reflecting the known co-morbidities of obesity, are present.
- In the remaining cases, there is insufficient information to identify a cause of death.

In order to demonstrate the safety of sibutramine the MAHs calculated a reporting incidence by means of the number of fatal cases related to exposure data. Based on this approach, a reporting incidence of 2.4 - 2.86 fatal events per 100,000 treatment years with sibutramine was calculated. This reporting rate is substantially lower than that derived from the best available "control" population: a BMI-matched cohort of patients derived from the large Nurse's Health Study (Manson et al. 1995), which calculated a fatality rate of 390 deaths per 100,000 treatment years.

From the reported fatal cases the CPMP recognised that the restrictions for use and warnings already described in the SPC for sibutramine containing medicinal products are disregarded to a certain extent. Therefore, the CPMP requests the MAHs to remind doctors of the importance of prescribing sibutramine in accordance to the SPC, through an appropriate "Dear Doctor Letter".

Other SPC changes based on the parallel evaluation of the current periodic safety update report No.8

Further to the CPMP assessment of the PSUR covering the period 12 May 2001 to 11 November 2001 (PSUR 8), the below mentioned changes have been made to the SPC. Information about these issues in this document will be given for reasons of complete information.

Bleeding disorders

Historically, reports of bleeding disorders have been received coincident with sibutramine therapy. Some reports were noted to be confounded. However, overall there is a significant number of suspected bleeding reactions, including vaginal bleeding disorders.

Sibutramine is a selective serotonin noradrenaline reuptake inhibitor. Selective Serotonin Reuptake Inhibitors (SSRIs) are known to be associated with haemorrhagic reactions. Whilst it is accepted that there may be a relationship between obesity and some menstrual disorders, there is a possibility that sibutramine is causally linked to cases of vaginal (and other) bleeding. Therefore, the SPC for sibutramine containing medicinal products should be amended as follows:

Section 4.4 - Special Warnings and special precautions for use

"In common with other agents that inhibit serotonin reuptake, there is a potential for an increased risk of bleeding in patients taking sibutramine. Sibutramine should, therefore, be used with caution in patients predisposed to bleeding events and those taking concomitant medications known to affect haemostasis or platelet function."

Gastrointestinal disorders

There have been reports of vomiting and diarrhoea. Vomiting and diarrhoea are recognised as class side-effects for SSRIs. Therefore, *"vomiting and diarrhoea"* should be included in section 4.8 of the SPC for sibutramine containing medicinal products.

Renal and urinary disorders

There have been reports of urinary retention, difficulty in micturition and dysuria coincident with sibutramine therapy. It is noted that some of these reports were associated with positive rechallenge. Urinary retention is a recognised side effect of SSRIs. Therefore, *"urinary retention"* should be included in section 4.8 of the SPC for sibutramine containing medicinal products.

Reproductive and breast disorders

In addition to menstrual disorders involving increased bleeding, there have been reports of other menstrual irregularities including amenorrhoea. In addition**,** there have been reports of male sexual dysfunction. Reproductive/sexual dysfunction are recognised side-effects of SSRIs/SNRIs. Therefore, *"abnormal ejaculation/orgasm, impotence and menstrual cycle disorders"* should be included in section 4.8 of the SPC for sibutramine containing medicinal products.

Immune system disorders

There have been reports (potentially life-threatening) of anaphylaxis, angioedema and other related serious allergic reaction (face oedema, tongue oedema). Therefore, the SPC for sibutramine containing medicinal products should be amended as follows:

Section 4.8 – Undesirable effects

"Allergic hypersensitivity reactions ranging from mild skin eruptions and urticaria to angioedema and anaphylaxis have been reported."

Overall conclusion on safety

Concerning safety, one of the main concerns is related to the potential cardiovascular risk of sibutramine. Sibutramine is known to increase the blood pressure and heart rate. According to the available data no new concerns with regards to the cardiovascular safety of sibutramine were identified. However, it cannot be excluded that sibutramine may have a relevant cardiovascular risk. Therefore cardiovascular adverse reactions should be closely monitored by the MAHs and the

previously requested cardiovascular outcome study (SCOUT) should be started. With regards to the reported fatal cases, no firm conclusion can be taken due to the heterogeneity of the causes of death, lack of data and in several cases due to the presence of alternative etiologies and complicating conditions.

Cases of depression have been reported in patients on sibutramine. Furthermore, suicide has been reported coincident with sibutramine in a small and unpredictable subpopulation of patients. Amendments to Sections 4.4 and 4.8 of the SPC have been made to reflect these events.

On the basis of the available data there is no evidence that sibutramine is associated with electrolyte imbalance and serotonin syndrome. Apart from the safety concerns above-mentioned, no other relevant safety concerns were identified.

OVERALL CONCLUSION ON BENEFIT/RISK

The efficacy data assessed by CPMP do not show any change of the overall benefit of sibutramine containing medicinal products since the conclusions reached by CPMP on the previous Article 12 referral. As demonstrated by body weight loss or decrease of BMI, sibutramine induces a relevant decrease of body weight in the context of low calorie diet and behaviour training programs. In addition, the available data also demonstrates that the use of sibutramine is associated with improvements in secondary outcome measures such as lipid profile and glycaemic control. On the basis of the available data the CPMP concluded that sibutramine is effective in the treatment of obesity.

One of the main safety concerns with sibutramine is related to potential cardiovascular risk, as sibutramine is known to increase blood pressure and heart rate. According to the available data no new concerns with regards to the cardiovascular safety of sibutramine were identified. However, it cannot be excluded that sibutramine may have a relevant cardiovascular risk. Therefore cardiovascular adverse reactions should be closely monitored by the MAHs and the previously requested cardiovascular outcome study (SCOUT) should be started. With regards to the reported fatal cases, no firm conclusion can be taken due to the heterogeneity of the causes of death, lack of data and in many cases due to the presence of alternative etiologies and complicating conditions.
Depression and suicidal events have been reported in a small and unpredictable subpopulation of patients on sibutramine therapy.
On the basis of the available data there is no evidence that sibutramine is associated with electrolyte imbalance and serotonin syndrome. Apart from the safety concerns above-mentioned, no other relevant safety concerns were identified.

Therefore the CPMP having reviewed the written responses from the MAHs and the rapporteurs' assessment report, considered that the benefit/risk balance of sibutramine containing medicinal products is favourable and the Marketing Authorisations should be maintained according to:

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

- Special Warnings
  Reinforcement of warnings with regards to psychiatric disorders, such as depression, suicide and suicide ideation.

- Undesirable effects
  Update of the section of undesirable effects with regards to psychiatric disorders.

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

- Clinical study (SCOUT)

The sibutramine cardiovascular outcome study (SCOUT) previously requested by CPMP should be started as soon as possible. The MAHs should present a timeline for the start of the study as well as for the submission of the interim and final results. This timeline should be presented to the CPMP within one month of the CPMP Opinion. As already previously requested by CPMP, 6-monthly updates on the progress of the study (safety and recruitment / drop-out rates) should be provided to CPMP. Interim results of the study should be provided at least two years after its start.

- 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.

- Dear Doctor Letter
  The MAHs should send a Dear Doctor Letter to remind doctors of the importance of prescribing sibutramine in accordance to the recommended SPC. This Dear Doctor Letter should be sent within one month of adoption of the CPMP Opinion.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND GROUNDS FOR THE CONDITIONS TO THE MARKETING AUTHORISATIONS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, for sibutramine containing medicinal products;

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

- The Committee agreed that there were some concerns related to the cardiovascular safety of sibutramine containing medicinal products, mainly in relation to increase in blood pressure and heart rate. However, the CPMP considered that the current contraindications and warnings in the Summary of Product Characteristics adequately address these safety concerns. There were also concerns with regards to psychiatric reactions and bleeding disorders related to the use of sibutramine.

- The Committee, as a consequence, 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 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 referred to in Annexes IA and IB 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

Note: This SPC is the one that was Annexed to the Commission Decision on this Article 31 referral for sibutramine containing medicinal products. The texts were valid at that time.

It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current texts.

1 TRADE NAME OF THE MEDICINAL PRODUCT

<Invented name>

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Hard capsule, capsule *(to be completed as appropriate)*

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

<Invented name> 10 mg / 15 mg 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:

<Invented name> 10 mg / 15 mg 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 *<Invented name> 10 mg / 15 mg* 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 *<Invented name>* is stopped. Patients should change their lifestyle while on *<Invented name>* 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 *<Invented name>* continued monitoring of the patient by the physician should be encouraged.

4.2 Posology and method of administration

Adults: The initial dose is one (1) capsule of *<Invented name>* 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 <*Invented name*> 10 mg (defined as less than 2 kg weight loss after four (4) weeks treatment), the dose may be increased to one (1) capsule of <*Invented name*> 15 mg once daily, provided that <*Invented name*> 10 mg was well tolerated.

Treatment must be discontinued in patients who have responded inadequately to <*Invented name*> 15 mg (defined as less than 2 kg weight loss after four (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, ie whose weight loss stabilises at less than 5% of their initial bodyweight or whose weight loss within three (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 <*Invented name*> *10mg / 15 mg* 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.

<*Invented name*> *10 mg / 15 mg* 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 *<Invented name> 10 mg / 15 mg*, 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 $\geq$ 10 bpm or systolic/diastolic blood pressure of $\geq$ 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 system”). 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.

- *<Invented name> 10 mg / 15 mg* 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, *<Invented name> 10 mg / 15 mg* should be used with caution in these patients.

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

- *<Invented name> 10 mg / 15 mg* 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 *<Invented name> 10 mg / 15 mg*.

- 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.

- Sibutramine should be given with caution to patients with open angle glaucoma and those who are at risk of raised intraocular pressure, e.g. family history.

- In common with other agents that inhibit serotonin reuptake, there is a potential for an increased risk of bleeding in patients taking sibutramine. Sibutramine should, therefore, be used with caution in patients predisposed to bleeding events and those taking concomitant medications known to affect haemostasis or platelet function.

- Cases of depression, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. Special attention is therefore required in patients with a history of depression. If signs or symptoms of depression occur during the treatment with sibutramine, the discontinuation of sibutramine and commencement of an appropriate treatment should be considered.

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 *<Invented name> 10 mg / 15 mg* 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), *<Invented name> 10 mg / 15 mg* should not be used concomitantly with other drugs which also raise serotonin levels in the brain.

Concomitant use of *<Invented name> 10 mg / 15 mg* 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 *<Invented name> 10 mg / 15 mg* to patients who use these medicines.

<Invented name> 10 mg / 15 mg 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 *<Invented name> 10 mg / 15 mg* 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 <*Invented name*> 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 <*Invented name*> *10 mg / 15 mg* 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 <*Invented name*> *10 mg / 15 mg*.

4.8 Undesirable effects

Most side effects reported with sibutramine 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 phase II/III clinical trials are listed below by body system (very common >1/10, common ≤1/10 and >1/100):

Body system	**Frequency**	**Undesirable effects**
Cardiovascular system (see detailed information below)	Common	Tachycardia Palpitations Raised blood pressure/hypertension Vasodilation (hot flush)
Gastrointestinal system	Very common	Constipation
	Common	Nausea Haemorrhoid aggravation
Central nervous system	Very common	Dry mouth Insomnia
	Common	Light-headedness Paraesthesia Headache Anxiety
Skin	Common	Sweating
Sensory functions	Common	Taste perversion

Cardiovascular system
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 special precautions.").

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

Clinically significant adverse events seen in clinical studies and during postmarketing surveillance are listed below by body system:

Blood and lymphatic system disorders:
Thrombocytopenia, Henoch-Schonlein purpura

Immune system disorders:
Allergic hypersensitivity reactions ranging from mild skin eruptions and urticaria to angioedema and anaphylaxis have been reported

Psychiatric disorders:
Depression in patients both with and without a prior history of depression (see section 4.4).

Nervous system disorders:
Seizures

Eye disorders:
Blurred vision

Gastrointestinal disorders:
Diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Rash, urticaria

Renal and urinary disorders:
Acute interstitial nephritis, mesangiocapillary glomerulonephritis, urinary retention

Reproductive system and breast disorders:
Abnormal ejaculation/orgasm, impotence, menstrual cycle disorders

Investigations:
Reversible increases in liver enzymes

Other:
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.

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-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}), adrenergic (β_1, β_2, β_3, α_1, α_2), dopaminergic (D_1-like, D_2-like), muscarinic, histaminergic (H_1), 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, ie 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, <*Invented name*> was shown to effect weight loss by enhancing satiety. Data are also available which demonstrate a thermogenic effect of <*Invented name*> by attenuating the adaptive decline in resting metabolic rate during weight loss. Weight loss induced by <*Invented name*> 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 HbA_{1c}. Similarly, in obese patients with dylipidaemia, weight loss was associated with increases in HDL choleseterol 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 (C_{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 C_{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

To be completed as appropriate.

6.2 Incompatibilities

To be completed as appropriate.

6.3 Shelf-life

To be completed as appropriate.

6.4 Special precautions for storage

To be completed as appropriate.

6.5 Nature and contents of container

To be completed as appropriate.

6.6 Instructions for use / handling

To be completed as appropriate.

7 Marketing authorization holder

To be completed as appropriate.

8 Marketing authorization number

To be completed as appropriate.

9. Date of first authorization/renewal of the authorization

To be completed as appropriate.

10. Date of revision of the text

To be completed as appropriate.

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

The sibutramine cardiovascular outcome study (SCOUT) previously requested by CPMP should be started as soon as possible. The MAHs should present a timeline for the start of the study as well as for the submission of the interim and final results. This timeline should be presented to the CPMP within one month of the CPMP Opinion.

As already previously requested by CPMP, 6-monthly updates on the progress of the study (safety and recruitment / drop-out rates) should be provided. Interim results of the study should be provided at least two years after its start.

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.

Dear Doctor Letter

The MAHs should send a Dear Doctor Letter to remind doctors of the importance to prescribe sibutramine in accordance to the recommended SPC. This Dear Doctor Letter should be sent within one month of adoption of the CPMP Opinion.

