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

London, 13 September 2002
EMEA/CPMP/2852/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
OPINION FOLLOWING AN ARTICLE 36 REFERRAL

SERTINDOLE

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

BACKGROUND INFORMATION

Sertindole is an atypical antipsychotic agent. It has affinity for dopamine receptors, especially D_2 and for serotinergic receptors: $5HT_{2A}$ and $5HT_{2C}$. It also inhibits α1-adrenergic receptors, but has almost no affinity to histaminergic or cholinergic receptors. Sertindole, indicated for the treatment of schizophrenia, was authorised in the United Kingdom in May 1996 and then subsequently in other European Member States through the Mutual Recognition procedure.

On 2 November 1998 the Netherlands presented to the EMEA a referral under article 36 of Directive 2001/83/EC, further to the suspension of the marketing of sertindole containing medicinal products in the Netherlands. The Netherlands considered that sertindole containing medicinal products presented a risk for public health due to an increased risk of sudden or cardiac death. The referral was considered by the CPMP at the November 1998 meeting and the referral procedure started on 18 November 1998.

The Marketing Authorisation Holders (MAHs) provided written explanations on 18 January and 25 May 1999 and oral explanations at the June 1999 CPMP meeting.

On 23 June 1999, the CPMP adopted an Opinion (CPMP/1784/99) recommending that the Marketing Authorisations for all sertindole containing medicinal products should be suspended for a one-year period. On the basis of the CPMP opinion, the European Commission adopted on 20 January 2000 a Decision suspending the Marketing Authorisations concerning medicinal products containing sertindole until 31 December 2000.

Subsequently, the CPMP, having reviewed the evidence submitted by the MAHs and having re-assessed the benefit/risk profile of sertindole containing medicinal products, adopted an opinion on 19 October 2000 recommending the renewal of the suspension of the Marketing Authorisations for all sertindole containing medicinal products for a further year. On 22 February 2001, the European Commission adopted a Decision suspending the Marketing Authorisations for medicinal products containing sertindole until 31 December 2001.

Supplementary information was provided by the MAHs on 18 May 2001 and on 31 May 2001.

On 28 June 2001, an Ad-Hoc Expert Group was convened to review the available clinical and pre-clinical data related to the cardiovascular activity of sertindole and to consider whether such data support the current marketing authorisation status of sertindole.

Supplementary information was provided by the MAHs on 15 august 2001, 28 September 2001 and 11 October 2001. Oral explanations were given by the MAHs on 16 October 2001.

Based on re-evaluation of all available data including additional data submitted by the MAHs on sertindole, it has been concluded that further clinical safety data, strong safeguards including extensive contraindications and warnings for patients at risk of cardiac dysrhythmias, a recommended reduction in maximum dose from 24 mg to 20 mg in all but exceptional cases, and extensive ECG monitoring requirement before and during treatment would permit the re-introduction of sertindole containing medicinal products to the market. In the first instance, reintroduction should be limited to patients participating in two new post-marketing studies. The MAHs are committed to perform these two post-marketing studies to further investigate the cardiovascular safety concern. Therefore, the CPMP

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considered that, on the basis of the currently available information, the benefit/risk balance of sertindole containing medicinal products is now favourable and recommended on 18 October 2001, the lifting of the suspension of the Marketing Authorisations for all medicinal products referred in Annex I of the CPMP Opinion on the following conditions:

- Amendment of the Summary of Product Characteristics as set out in Annex III of the CPMP Opinion.
- The CPMP requirements and the conditions of the marketing authorisations as set out in Annex IV of the CPMP Opinion.

On the basis of the CPMP Opinion, the European Commission issued a Decision on 26 June 2002 concerning the lifting of the suspension of the Marketing Authorisations for sertindole containing medicinal products.

ANNEX I
LIST OF THE NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDERS, STRENGTHS, PHARMACEUTICAL FORMS, ROUTE OF ADMINISTRATION, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES SERTINDOLE 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
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4 mg Filmtabletten	4 mg	film coated tablet	Oral use	blister Polypropylene container	30 100
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 8 mg Filmtabletten	8 mg	film coated tablet	Oral use	blister Polypropylene container	28 100
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 12 mg Filmtabletten	12 mg	film coated tablet	Oral use	blister Polypropylene container	28 100
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16 mg Filmtabletten	16 mg	film coated tablet	Oral use	blister Polypropylene container	28 100
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg Filmtabletten	20 mg	film coated tablet	Oral use	blister Polypropylene container	28 100

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 24 mg Filmtabletten	24 mg	film coated tablet	Oral use	blister Polypropylene container	28 100
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use	blister Polypropylene container	20, 28, 30 50, 98, 100 100
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use	Blister Polypropylene container	20, 28, 30, 50, 98, 100 100
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use	Blister Polypropylene container	20, 28, 30 50, 98, 100 100

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use	blister Polypropylene container	20, 28, 30 50, 98, 100 100
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use	blister Polypropylene container	20, 28, 30 50, 98, 100 100
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use	Blister Polypropylene container	20, 28, 30, 50, 98, 100 100
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use	blister polypropylene container	30 100
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use	Not applicable	Not applicable

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use	blister polypropylene container	28 100
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use	blister polypropylene container	28 100
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use	blister polypropylene container	28 100
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use	Not applicable	Not applicable
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 4mg	4 mg	film coated tablet	Oral use	blister	20 100 (5 X 20)

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 8mg	8 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 12mg	12 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 16mg	16 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 20mg	20 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 24mg	24 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4mg	4 mg	film coated tablet	Oral use	blister	20 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 8mg	8 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 12 mg	12 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16mg	16 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg	20 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 24 mg	24 mg	film coated tablet	Oral use	blister	20 50 100 (5 x 20)
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	4 mg	film coated tablet	Oral use	blister	30
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	8 mg	film coated tablet	Oral use	blister	20 28
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	12 mg	film coated tablet	Oral use	blister	20 28
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	16 mg	film coated tablet	Oral use	blister	20 28
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	20 mg	film coated tablet	Oral use	blister	20 28

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	24 mg	film coated tablet	Oral use	blister	20 28
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use	blister polypropylene container	20, 28, 30, 50, 98, 100 100
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	4 mg	film coated tablet	Oral use	blister	30
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	12 mg	film coated tablet	Oral use	blister	28

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	16 mg	film coated tablet	Oral use	blister	28
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	20 mg	film coated tablet	Oral use	blister	28
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4 mg	4 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 8 mg	8 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 12 mg	12 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16 mg	16 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg	20 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 24 mg	24 mg	film coated tablet	Oral use	blister polyproylene container	20, 28, 30, 50, 98, 100 100
Portugal	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	coated tablet	Oral use	blister	30
Portugal	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	coated tablet	Oral use	blister	28
Portugal	H. Lundbeck A/S Ottiliavej 9	Serdolect	16 mg	coated tablet	Oral use	blister	28

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
	Valby DK-2500 Copenhagen- Denmark						
Portugal	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	coated tablet	Oral use	blister	28
Spain	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use	blister	30 98
Spain	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use	blister	28
Spain	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use	blister	28

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Spain	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use	blister	28
Spain	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use	blister	28
Spain	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use	blister	28
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use	blister Polypropylene container	20, 28, 30, 50, 98, 100 100
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	Film coated tablet	Oral use	Blister Polypropylene container	20, 28, 30, 50, 98, 100 100

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use	blister Polypropylene container	20, 28, 30, 50, 98, 100 100
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use	blister Polypropylene container	20, 28, 30, 50, 98, 100 100
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use	blister Polypropylene container	20, 28, 30, 50, 98, 100 100
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	Film coated tablet	Oral use	Blister Polypropylene container	20, 28, 30, 50, 98, 100 100

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR LIFTING OF THE SUSPENSION OF THE MARKETING AUTHORISATIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SERTINDOLE CONTAINING MEDICINAL PRODUCTS

The cardiac safety of sertindole was first brought into question in 1998, when the reporting rate of sudden unexplained death and cardiac arrhythmia associated with sertindole (through the UK ADROIT database) was noted to be higher than for other atypical antipsychotics. This signal ultimately led the Netherlands to suspend the Marketing Authorisations and to refer the matter to the CPMP for binding arbitration under Article 15a of Council Directive 75/319/EEC, as amended.

Following the Article 15a referral, the Marketing Authorisations was suspended in the EU on 20 January 2000 and subsequently the suspension was renewed on 22 February 2001, because of concerns regarding the risk of serious cardiovascular adverse reactions such as prolongation of QT interval, arrhythmia and sudden deaths. In view of this and because sertindole had not been demonstrated to offer greater therapeutic efficacy than other alternative compounds, the overall risk/benefit balance was considered unfavourable.

Since the initial assessment, the MAHs have submitted additional pre-clinical and epidemiological data and have proposed that sertindole be reintroduced.

On 28 June 2001, an Ad-Hoc Expert Group was convened to review the addtional data available. It was considered that the additional preclinical studies did not support an arrhythmogenic effect as predicted from QT prolongation alone. Nor did the additional clinical data show a torsadogenic effect, or an effect on syncope or dizziness as proxy for serious ventricular arrhythmias. The results from observational studies neither support the original safety signal observed from spontaneous reporting, nor provide sufficient evidence to refute this safety signal. Overall the majority of the members of the Ad-Hoc Expert Group expressed the opinion that the cardiac toxicity of sertindole did not preclude its re-introduction to the market with the provision of strong safeguards excluding patients at risk and with commitment by the MAHs to perform further clinical studies post-authorisation.

The conclusions of the Ad-Hoc Expert Group (CPMP/1850/01) were adopted by the CPMP during its July 2001 meeting. The MAHs were invited to submit detailed proposals regarding the possible re-introduction of sertindole to the market. The MAHs submitted supporting documentation for the lifting of the suspension of sertindole containing medicinal products on 15 August 2001, and responded to the request for supplementary information on 28 September 2001, and provided the revised protocol for the randomised study on 11 October 2001.

All additional data received were reviewed, assessed and discussed by the CPMP as part of the review of the one-year suspension of sertindole containing medicinal products. The main issues discussed as well as the conclusions of the CPMP are described below.

Overall conclusion on benefit/risk

From the data on efficacy, sertindole is effective for the treatment of schizophrenic patients.

Regarding safety, sertindole is associated with a dose-dependent increases in QT interval. However, additional preclinical data did not support an arrhythmogenic effect as predicted from QT prolongation alone. The signal of an elevated risk of cardiac death and increased all-cause-mortality rate with the use of sertindole was neither confirmed nor refuted by further observational studies.

Based on re-evaluation of all available data including additional data submitted by the MAHs on sertindole, it has been concluded that further clinical safety data, strong safeguards and increase ECG monitoring requirements would permit the re-introduction of sertindole containing medicinal products to the market.

The MAHs commit to perform two post-marketing studies to further investigate the cardiovascular safety concern.

Therefore, the CPMP considered that, on the basis of the currently available information, the benefit/risk balance of sertindole containing medicinal products is favourable and the suspension of the Marketing Authorisations could be lifted under the following conditions:

1. Amendment of the Summary of Product Characteristics as set out in Annex III of the CPMP Opinion with emphasis on the following:
   - *Therapeutic Indications* (section 4.1) - Sertindole is indicated for the treatment of schizophrenia. Due to cardiovascular safety concerns, sertindole should only be used for patients intolerant to at least one other antipsychotic agent. Sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients.
   - *Maximum dosage* (section 4.2) - Sertindole produces dose-dependent QT prolongation in normal clinical usage. Therefore the maximum recommended dose has been limited to 20 mg daily. Only in exceptional cases should 24 mg maximum dose be considered during maintenance therapy.
   - *Special warnings* (section 4.3) – Reinforcement of warnings with regard to the ECG monitoring and screening for at-risk patients.

2. The CPMP requirements as set out in Annex IV of the CPMP Opinion with regard to:
   1) The MAHs wil ensure that all patients treated with sertindole will be exclusively enrolled in studies for the first year, in agreement with the CPMP, after publication of the Commission decision to lift the suspension based on the Article 15a referral.
      After one year, the MAHs will, based on the CPMP recommendation after the review of the study information made available by the Independent Safety Board, prolong this commitment if the study information warrants this.
   2) Final study protocols will be submitted by the MAHs by 25 October 2001 to the CPMP for approval.
   3) The MAHs will provide to the CPMP semi-annual study update reports on the progress of the study (Total recruitment, total number of deaths / hospitalisations, drop-out rates). These reports will be included with 6-month PSURs. PSURs will continue at 6-month intervals for three years and then the periodicity will be reviewed by the CPMP.
   4) The MAHs will not initiate the marketing and launch activities in this period of sertindole containing medicinal products outside the conditions laid down under 1).

GROUNDS FOR LIFTING OF THE SUSPENSION OF THE MARKETING AUTHORISATIONS

Whereas

- The Committee considered that the additional preclinical studies did not support an arrhythmogenic effect as predicted from QT prolongation alone. Nor did the additional clinical data show a torsadogenic effect, or an effect on syncope or dizziness as proxy for serious ventricular arrhythmias.
- The Committee considered that the results from observational studies neither support the original safety signal observed from spontaneous reporting (i.e. higher reporting rate of sudden unexplained death and fatal cardiac adverse drug reactions than for other atypical antipsychotics), nor provide evidence to refute this safety signal.
- The Committee agreed that sertindole is effective in schizophrenic patients.
- The Committee, on the basis of the currently available information provided by the MAHs, considered the benefit/risk balance of sertindole containing medicinal products is favourable.

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

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

See Annex I.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 mg tablet contains:	sertindole 4 mg
Each 8 mg tablet contains:	sertindole 8 mg
Each 12 mg tablet contains:	sertindole 12 mg
Each 16 mg tablet contains:	sertindole 16 mg
Each 20 mg tablet contains:	sertindole 20 mg
Each 24 mg tablet contains:	sertindole 24 mg

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Description of tablets:

4 mg: Oval, white, biconvex tablets marked with "S4" on one side
8 mg: Oval, white, biconvex tablets marked with "S8" on one side
12 mg: Oval, white, biconvex tablets marked with "S12" on one side
16 mg: Oval, white, biconvex tablets marked with "S16" on one side
20 mg: Oval, white, biconvex tablets marked with "S20" on one side
24 mg: Oval, white, biconvex tablets marked with "S24" on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sertindole is indicated for the treatment of schizophrenia.

Due to cardiovascular safety concerns, sertindole should only be used for patients intolerant to at least one other antipsychotic agent.

Sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients.

4.2 Posology and method of administration

Sertindole is administered orally once daily with or without meals. In patients where sedation is required, a benzodiazepine may be co-administered.

Note: ECG monitoring is required before and during treatment with sertindole: see section 4.4.

Titration
All patients should be started on sertindole 4 mg/day. The dose should be increased by increments of 4 mg after 4-5 days on each dose until the optimal daily maintenance dose within the range of 12-20 mg is reached. Due to the α_1-blocking activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period. A starting dose of 8 mg or a rapid increase in dose carries a significantly increased risk of postural hypotension.

Maintenance
Dependent on individual patient response, the dose may be increased to 20mg/day. Only in exceptional cases should the maximum dose of 24mg be considered, as clinical trials have not demonstrated consistently improved efficacy above 20mg and QT prolongation may be increased at the upper end of the dose range.

The blood pressure of the patients should be monitored during titration and early maintenance treatment.

Elderly
A pharmacokinetic study showed no difference between young and elderly subjects. However, only limited clinical trial data exist for patients greater than 65 years of age. Therefore, until further clinical experience is available, sertindole should be used with care in the elderly. Slower titration and lower maintenance doses may be appropriate in elderly patients.

Children and adolescents under the age of 18
The safety and efficacy of sertindole in children and adolescents have not been established.

Reduced renal function
Sertindole can be given at the usual dosage to patients with renal impairment (see section 4.3). The pharmacokinetics of sertindole is not affected by haemodialysis.

Reduced hepatic function
Patients with mild/moderate hepatic impairment require slower titration and a lower maintenance dose.

Re-titration of sertindole in patients for whom treatment has previously been discontinued
When restarting sertindole treatment in patients who have had an interval of less than one week without sertindole, re-titration of sertindole is not required and their maintenance dose can be re-introduced. Otherwise the recommended titration schedule should be followed. An ECG should be taken prior to re-titration of sertindole.

Switching from other antipsychotics
Treatment with sertindole can be initiated according to the recommended titration schedule concomitantly with cessation of other oral antipsychotics. For patients treated with depot antipsychotics, sertindole is initiated in place of the next depot injection.

4.3 Contra-indications

Hypersensitivity to sertindole or any of the excipients.

Sertindole is contraindicated in patients with known uncorrected hypokalaemia, and those with known uncorrected hypomagnesaemia.

Sertindole is contraindicated in patients with a history of clinically significant cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia (<50 beats per minute).

Furthermore, sertindole should not be initiated in patients with congenital long QT syndrome or a family history of this disease, or in patients with known acquired QT interval prolongation (QTc above 450 msec in males and 470 msec in females).

Sertindole is contraindicated in patients receiving drugs known to prolong the QT interval. Relevant classes include:
- class Ia and III antiarrhythmics (e.g., quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g., thioridazine)
- some macrolides (e.g., erythromycin)
- some antihistamines (e.g., terfenadine)

- some quinolone antibiotics (e.g., gatifloxacin)

The above list is not exhaustive and other individual drugs known to increase QT interval (e.g., cisapride, lithium) are also contraindicated.

Co-administration of sertindole is contraindicated with drugs known to potently inhibit hepatic cytochrome P450 3A enzymes (see section 4.5). Relevant classes include:
- systemic treatment with 'azole' antifungal agents (e.g., itraconazole)
- macrolide antibiotics (e.g., erythromycin)
- HIV protease inhibitors (e.g., indinavir)

The above list is not exhaustive and other individual drugs known to potently inhibit CYP3A enzymes (e.g., cimetidine) are also contraindicated.

Sertindole is contraindicated in patients with severe hepatic impairment.

4.4 Special warnings and special precautions for use

Cardiovascular

Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Prolongation of the QTc interval in some drugs is associated with the ability to cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death. However, clinical and non-clinical data have been unable to confirm whether sertindole is more arrhythmogenic than other antipsychotics. Sertindole should therefore only be used for patients intolerant to at least one other antipsychotic agent.

ECG monitoring:
- ECG monitoring is mandatory prior to and during treatment with sertindole. ECG monitoring is ideally conducted in the morning and the Bazett or Fridericia formulae for QTc calculation are preferred.
- ECG monitoring should be conducted at baseline: sertindole is contraindicated if a QTc interval of more than 450 msec in males or 470 msec in females is observed.
- Upon reaching steady state after approximately 3 weeks or when reaching 16 mg, a further ECG should be taken.
- During maintenance treatment, ECG measurements should take place prior to and after any increase in dose. If a QTc interval of more than 500 msec is observed during treatment with sertindole, it is recommended that treatment with sertindole be discontinued. For patients experiencing symptoms such as palpitations, convulsions, or syncope that could indicate the occurrence of arrhythmias, the prescriber should initiate urgent evaluation, including ECG.
- An ECG is recommended after the addition or increase of dosage of concomitant medication that may increase the sertindole concentration (see section 4.5).

The risk of QT prolongation is increased in patients receiving concomitant treatment with drugs that prolong the QTc interval or drugs that inhibit sertindole metabolism (see section 4.3).

Baseline serum potassium and magnesium levels should be measured before commencing treatment with sertindole in patients at risk of significant electrolyte disturbances. Low serum potassium and magnesium should be corrected before proceeding with treatment. Monitoring of serum potassium is recommended for patients experiencing vomiting, diarrhoea, treatment with potassium-depleting diuretics, or other electrolyte disturbances.

In view of the increased risk of significant cardiovascular disease in the elderly, sertindole should be used with care in this population (see section 4.2).

Due to the α_1-blocking activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period.

Antipsychotic drugs may inhibit the effects of dopamine agonists. Sertindole should be used cautiously in patients with Parkinson's disease.

Some SSRIs, like fluoxetine and paroxetine (potent CYP2D6 inhibitors), may increase the plasma levels of sertindole by a factor of 2 to 3 (see section 4.5).

Reduced hepatic function
Patients with mild/moderate hepatic dysfunction should be closely observed. Slower titration and a lower maintenance dose are recommended.

Tardive dyskinesia
Tardive dyskinesia is thought to be caused by dopamine receptor hypersensitivity in the basal ganglia as a result of chronic receptor blockade by antipsychotics. A low incidence (comparable to that of placebo) of extrapyramidal symptoms during treatment with sertindole has been seen in clinical studies. However, long-term treatment with antipsychotic compounds (especially at high dosages) is associated with the risk of tardive dyskinesia. If signs of tardive dyskinesia appear, dosage reduction or drug discontinuation should be considered.

Seizures
Sertindole should be used with caution in patients with a history of seizures.

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. The management of NMS should include immediate discontinuation of antipsychotic drugs.

4.5 Interaction with other medicinal products and other forms of interaction

Increases in the QT interval related to sertindole treatment may be exacerbated by the co-administration of other drugs known to increase the QT interval. Co-administration of such drugs is therefore contraindicated (see section 4.3).

Sertindole is extensively metabolised by the CYP2D6 and CYP3A isozymes of the cytochrome P450 system. CYP2D6 is polymorphic in the population and both isozymes can be inhibited by a variety of psychotropic and other drugs.

CYP2D6
The plasma concentration of sertindole is increased by a factor of 2-3 in patients concurrently taking fluoxetine or paroxetine (potent CYP2D6 inhibitors), thus a lower maintenance dose of sertindole may be required. Although not investigated, comparable effects are expected for quinidine (potent CYP2D6 inhibitor), which in addition is known to prolong the QT interval (see section 4.3). Other potential CYP2D6 inhibitors (such as sertraline, tricyclic antidepressants, and propranolol) do not appear to influence the plasma concentration of sertindole. *In vitro* studies have shown that high concentrations of sertindole and its major metabolites inhibit the activity of CYP2D6. Sertindole is proposed to be a weak inhibitor of CYP2D6 substrates since the dextromethorphan metabolic ratio was only slightly affected during sertindole treatment.

Substrates of the CYP2D6 isozyme include β-blockers, antiarrhythmic agents, some antihypertensives, and a large number of neuroleptics and antidepressants. CYP2D6 is markedly inhibited by quinidine, fluoxetine, and paroxetine.

CYP3A
Of the interactions detected for CYP3A substrates, none are of sufficient magnitude to be clinically significant. Minor increases (<25%) in sertindole plasma concentrations have been noted for macrolide antibiotics (e.g., erythromycin, a CYP3A inhibitor) and calcium channel antagonists (weak CYP3A inhibitors). In CYP2D6 poor metabolisers, the inhibitory effect could be larger, since elimination of sertindole by both CYP2D6 and CYP3A would be affected. Ketoconazole and itraconazole are both very strong inhibitors of CYP3A (see section 4.3).

Substrates of the CYP3A isozyme include immunomodulators, calcium channel blockers, and class III antiarrhythmic agents. The most well known inhibitors of CYP3A are cimetidine, azole antifungal agents, HIV protease inhibitors, and macrolide antibiotics. Co-administration of sertindole with CYP3A inhibitors is contraindicated as this may lead to significant increases in sertindole levels (see section 4.3).

The metabolism of sertindole is significantly enhanced by agents known to induce CYP isozymes, notably carbamazepine and phenytoin, which can decrease the plasma concentrations of sertindole by a factor of 2 to 3. Reduced antipsychotic efficacy in patients receiving these drugs or other inducing agents may require the dose of sertindole to be adjusted to the upper dosage range.

4.6 Pregnancy and lactation

Pregnancy
The safety of sertindole for use during pregnancy has not been established.

Sertindole was not teratogenic in animal reproduction studies. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (see section 5.3).

Consequently, sertindole should not be used during pregnancy.

Lactation
Studies in nursing mothers have not been performed, however, it is expected that sertindole will be excreted in breast milk.

If treatment with sertindole is considered necessary, discontinuation of breast-feeding should be considered.

4.7 Effects on ability to drive and use machines

Sertindole is not sedative, however, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Side effects
In clinical trials, adverse events with an incidence greater than 1% associated with the use of sertindole and significantly different from placebo were (listed in order of decreasing frequency): rhinitis/nasal congestion, abnormal ejaculation (decreased ejaculatory volume), dizziness, dry mouth, postural hypotension, weight gain, peripheral oedema, dyspnoea, paraesthesia, and prolonged QT interval (see section 4.4).

Extrapyramidal Symptoms (EPS)
The incidences of patients treated with sertindole reporting EPS-related adverse events were similar to those of patients treated with placebo. In addition, in placebo-controlled clinical trials, the percentage of sertindole-treated patients requiring anti-EPS medication was indistinguishable from that of placebo-treated patients.

Some of the adverse drug reactions will appear at the beginning of treatment and disappear with continuous treatment, e.g., postural hypotension.

The table below shows adverse reactions sorted by system organ class and frequency:
Very common (>10%)
Common (1-10%)
Uncommon (0.1-1%)
Rare (0.01-0.1%)
Very rare (<0.01%)

Metabolism and nutritional disorders	
Uncommon	hyperglycemia
Nervous system disorders	
Common	dizziness, paraesthesia
Uncommon	syncope, convulsion, movement disorder (in particular tardive dyskinesia, see section 4.4)
Cardiac disorders	
Common	peripheral oedema
Uncommon	Torsade de Pointes (see section 4.4)
Vascular disorders	
Common	postural hypotension (see section 4.4)
Respiratory, thoracic and mediastinal disorders	
Very common	rhinitis/nasal congestion
Common	dyspnoea
Gastrointestinal disorders	
Common	dry mouth
Reproductive system and breast disorders	
Common	abnormal ejaculation (decreased ejaculatory volume)
Investigations	
Common	weight gain, prolonged QT interval, red blood cells urine positive, white blood cells urine positive

4.9 Overdose

Experience with sertindole in acute overdose is limited. Fatal cases have occurred. However, patients taking estimated dosages up to 840 mg have recovered without sequelae. Reported signs and symptoms of overdose were somnolence, slurred speech, tachycardia, hypotension, and transient prolongation of the QTc interval. Cases of Torsade de Pointes have been observed, often in combination with other drugs known to induce TdP.

Treatment
In case of acute overdose, establishment of an airway and maintenance of adequate oxygenation should be ensured.

Continuous monitoring of ECG and vital signs should commence immediately. If the QTc interval is prolonged, it is recommended that the patient be monitored until the QTc interval has normalised. A half-life of sertindole of 2 to 4 days should be taken into account.

Intravenous access should be established, and the administration of activated charcoal with laxative should be considered. The possibility of multiple drug involvement should be considered.

There is no specific antidote to sertindole, and it is not dialysable, therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, adrenaline and dopamine should be used with caution, since β stimulation combined with α_1 antagonism associated with sertindole may worsen hypotension.

If antiarrhythmic therapy is administered, agents such as quinidine, disopyramide, and procainamide carry a theoretical hazard of QT interval-prolonging effects that might be additive to those of sertindole.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: limbic selective antipsychotics, ATC-code: N05A E 03

It has been proposed that the neuropharmacological profile of sertindole, as an antipsychotic drug, is derived from its selective inhibitory effect on mesolimbic dopaminergic neurons and is due to balanced inhibitory effects on central dopamine D_2 and serotonin $5HT_2$ receptors as well as on α_1-adrenergic receptors.

In animal pharmacology studies, sertindole inhibited spontaneously active dopamine neurons in the mesolimbic ventral tegmental area (VTA) with a selectivity ratio of more than 100 compared to dopamine neurons in substantia nigra pars compacta (SNC). Inhibition of SNC activity is thought to be involved in movement side effects (EPS) associated with many antipsychotic drugs.

Antipsychotic drugs are known to increase serum prolactin levels through dopamine blockade. The prolactin levels in patients receiving sertindole remained within normal limits, both in short-term studies and during long-term treatment (one year).

Sertindole has no effect on muscarinic and histaminic H_1 receptors. This is confirmed by the absence of anticholinergic and sedative effects related to those receptors.

5.2 Pharmacokinetic properties

Elimination of sertindole occurs via hepatic metabolism, with a mean terminal half-life of approximately 3 days. The clearance of sertindole decreases with multiple dosing to a mean around 14 l/h (females have approximately 20% lower apparent clearance than males, although lean-mass corrected clearances are comparable). Therefore, upon multiple dosing, accumulation is greater than predicted from a single dose, due to an increase in the systemic bioavailability. However, at steady state, clearance is dose independent and plasma concentrations are proportional to dose. There is moderate inter-subject variability in sertindole pharmacokinetics, due to the polymorphism in the cytochrome P450 2D6 (CYP2D6). Patients who are deficient in this hepatic enzyme have sertindole clearances that are ½ to 1/3 of those who are CYP2D6 extensive metabolisers. These poor metabolisers (up to 10% of the population) will therefore have plasma levels 2-3 times the normal. Sertindole concentration is not predictive of therapeutic effect for an individual patient; thus, dosing individualisation is best achieved by assessment of therapeutic effect and tolerability.

Absorption

Sertindole is well absorbed with a t_{max} of sertindole after oral administration of approximately 10 hours. Different dose strengths are bioequivalent. Food and aluminium-magnesium antacids have no clinically significant effect on the rate or the extent of sertindole absorption.

Distribution
The apparent volume of distribution (V_β/F) of sertindole after multiple dosing is approximately 20 l/kg. Sertindole is about 99.5% bound to plasma proteins, primarily to albumin and α_1-acid glycoprotein. In patients treated with recommended doses, 90% of the measured concentrations are below 140 ng/ml (~320 nmol/l). Sertindole penetrates into red blood cells with a 1.0 blood/plasma ratio. Sertindole readily penetrates the blood-brain and placental barriers.

Metabolism
Two metabolites have been identified in human plasma: dehydrosertindole (oxidation of the imidazolidinone ring) and norsertindole (N-dealkylation). Concentrations of dehydrosertindole and norsertindole are approximately 80% and 40%, respectively, of the parent compound at steady state. Sertindole activity is primarily due to the parent drug and the metabolites do not appear to have significant pharmacological effects in humans.

Excretion
Sertindole and its metabolites are eliminated very slowly, with a total recovery of 50-60% of a radiolabelled oral dose 14 days after administration. Approximately 4% of the dose is excreted into the urine as parent drug plus metabolites of which less than 1% is present as parent drug. Faecal excretion is the major route of excretion and accounts for the rest of the parent drug and metabolites.

5.3 Preclinical safety data

QT prolongation on the ECG, possibly due to inhibition of the delayed rectifier potassium channel (I_{Kr}, HERG), has been observed in animal studies. However, sertindole shows absence of early after-depolarisations in cardiac rabbit and dog purkinje fibres. Early after-depolarisations are considered essential to trigger Torsade de Pointes. Sertindole did not induce Torsade de Pointes ventricular arrhythmias in atrio-ventricular node ablated rabbit hearts, despite experimental introduction of severe hypokalaemia (1.5 mmol) and bradycardia. However, the extrapolation of animal findings to humans with regard to QT prolongation and arrhythmia must be undertaken with caution as significant inter-species differences may exist.

The acute toxicity of sertindole is low. In chronic toxicity studies in the rat and dog (3-5 times clinical exposure), several effects were observed. These effects are in line with the pharmacological properties of the drug.

Animal reproduction studies have not given evidence of teratogenic effects. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (0.2 mg/kg/day), and at higher dosages, a decreased pup survival in the early lactation period, reduced weight gain, and delayed development of pups in doses producing maternal toxicity.

Mating and fertility were affected in adult male rats at dosages of 0.14 mg/kg/day and above. The adult fertility impairment, which was reversible, was ascribed to the pharmacological profile of sertindole.

Sertindole was not toxic in a battery of *in vitro* and *in vivo* genotoxicity studies. Carcinogenicity studies conducted in the mouse and rat did not indicate any development of tumours relevant to the clinical use of sertindole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Maize starch, lactose monohydrate, hydroxypropylcellulose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, macrogol 400.

Tablet coating
Hydroxypropylmethylcellulose, titanium dioxide (E171), macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

- PVC/PVdC laminate (clear or white) blister with aluminium foil, inside a carton blackened on the inside, containing 20, 28, 30, 50, 98, or 100 tablets.
- Grey polypropylene container of 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special precautions.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION HOLDER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

Conditions of the Marketing Authorisations

CPMP requirements in relation to post-marketing data

1. The MAHs commit to ensuring that all patients treated with sertindole will be accounted for and exclusively enrolled in studies for the first year, in agreement with the CPMP, after publication of the Commission decision to lift the suspension based on the Article 15a referral.

   After one year, the MAHs will, based on the CPMP recommendation after the review of the study information made available by the Independent Safety Board, prolong this commitment if the study information warrants this.

2. Final study protocols will be submitted by the MAHs by 25 October 2001 to the CPMP for approval.

3. The MAHs will commit to semi-annual study updates to the CPMP on the progress of the study. These reports will be included with 6-month PSURs. PSURs will continue at 6-month intervals for three years and then the periodicity will be reviewed by the CPMP.

4. The MAHs will not initiate the marketing and launch activities in this period of sertindole containing medicinal products outside the conditions laid down under 1.

