Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended

Solian
(Amisulpride)

IE/W/0009/pdWS/001

<table>
<thead>
<tr>
<th>Rapporteur:</th>
<th>Ireland</th>
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<tr>
<td>Finalisation procedure (day 120):</td>
<td>04/09/2013</td>
</tr>
<tr>
<td>Date of finalisation of PAR</td>
<td>29/11/2013</td>
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## ADMINISTRATIVE INFORMATION

<table>
<thead>
<tr>
<th>Invented name of the medicinal product(s):</th>
<th>Solian</th>
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<tbody>
<tr>
<td>INN (or common name) of the active substance(s):</td>
<td>Amisulpride</td>
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<tr>
<td>MAH (s):</td>
<td>Sanofi-Aventis</td>
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<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>NO5AL05</td>
</tr>
</tbody>
</table>
| Pharmaceutical form(s) and strength(s): | 50, tablets  
100, tablets  
200, tablets  
400 film-coated tablets |
I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

Summary of outcome

☑ No change
☐ Change
☐ New study data: <section(s) xxxx, xxxx>

RECOMMENDATION

The MAH has provided a review of the use of amisulpride in children and adolescents which is of good quality. The available data are inadequate to make an evaluation of clinical benefit, if any. The safety profile is consistent with that in adults and is appropriately described in the product information. No further regulatory action is necessary.

II. INTRODUCTION

According to Articles 45 and 46 of Regulation (EC) No. 1901/2006, the CMD(h) and the EMA require that for authorised medicinal products, paediatric studies not previously submitted should be submitted for assessment to European Health Agencies. In accordance with the Paediatric Regulation and specifically with the Best Practice Guide Article 45 – Paediatric Regulation/EU Work-sharing procedure dated September 2008 and updated in July 2010, any paediatric studies completed before 26 January 2007 shall be submitted by the Marketing Authorization Holders (MAH) for assessment. The MAH is expected to submit all data, including published information relevant for the paediatric assessment; a short critical expert overview should be added clarifying the context of the data and relevance for EU situation.

On July 19th 2012, Sanofi was informed by the EMA/CMD(h) about the initiation of the work-sharing procedure concerning Article 45 for amisulpride and has been requested to submit within one month the paediatric studies to the attention of the appointed Rapporteur (Ireland).

The Critical Expert Overview has been prepared in order to address this request. Data submitted via line-listings in January and April 2008 when relevant, are described in the overview. Additional internal or published data relevant for the current procedure are also presented, on the basis of a review of Sanofi sponsored clinical studies, internal pharmacovigilance data, and a literature search of the Medline and Embase databases using ‘amisulpride’ as a keyword.

Regulatory history

Amisulpride was originally approved in France in January 1986 and is currently registered in 24 EU countries by national procedure, in the main indication of schizophrenia. The 50 mg dosage is also registered in the dysthymia indication in 3 EU countries by national procedures (Czech Republic, Italy and Portugal).

1 The recommendation from section V can be copied in this section.
The first PSUR procedure under the EU PSUR synchronisation scheme (Procedure number: IE/H/PSUR/0017/001) was initiated in April 2009 with the Irish Medicines Board (IMB) as PSUR-Reference Member State (P-RMS) and covered a period from 01-feb-2006 to 31-jan-2009.

Following the Preliminary Assessment Report issued on 18 May 2009, a Clinical Overview “Paediatric use” had been provided, in order to review clinically relevant information concerning the efficacy and safety of amisulpride in the treatment of schizophrenia in adolescents, from puberty to the age of 18 years.

The amisulpride PSUR Worksharing procedure was completed on 15 December 2009 with the issue of the Final Assessment Report with an agreed Core Safety Profile (CSP). Based on the submitted Clinical Overview, the following paediatric statements have been endorsed in the CSP:

• Section 4.2 Posology and method of administration:

Children: The efficacy and safety of amisulpride from puberty to the age of 18 years have not been established: There are limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, the use of amisulpride from puberty to the age of 18 years is not recommended; in children up to puberty amisulpride is contraindicated (see section: 4.3).

• Section 4.3 Contraindications

Children till puberty

As a consequence, national variations have been submitted in all EU countries to implement the agreed CSP.

An ongoing cycle 2 procedure of the PSUR EU Worksharing (procedure number: IE/H/PSUR/0017/002) covering period from 01-Feb-2009 to 31-Jan-2012 was initiated in March 2012, and is also assessed by the IMB.

The MAH stated that the submitted paediatric studies do influence the benefit risk for Solian and that there is no consequential need for regulatory action.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical studies

Solian is presented as; 50 mg, 100 mg, 200 mg tablets and 400 mg film-coated tablets and oral solution 100 mg/mL.

III.2 Non-clinical aspects

An expert report on the toxicological and pharmacological documentation pertaining to amisulpride was written by SZ Langer in 1997. No non-clinical studies were specifically performed in juvenile animals. A review of literature based on Embase and Medline databases was made; the search terms were amisulpride combined with (juvenile or newborn or postnatal development or immaturity or pup (rodent), limited to animal data. An additional search was performed in Toxnet/Dart database (Developmental and Reproductive Toxicology Database). No relevant data supportive of paediatric use have been found.
3. Discussion on non clinical aspects

Amisulpride has been in clinical use since 1986 accordingly the MAH has not generated any recent new pre-clinical data – this is acceptable.

III.3 Clinical aspects

1. Introduction

Schizophrenia is a severe chronic mental illness characterised by abnormal thought processes which may present as delusions, auditory hallucinations, thought insertion, aberrant inferential judgements or paranoia, accompanied by mood abnormalities, in particular flattened affect. The clinical course is variable but generally involves recurrent episodes of psychosis separated by improvements but in which social functioning usually remains impaired. Functional status usually deteriorates over the course of the disease. About 10% of patients with schizophrenia experience acute agitation accompanied by violent or destructive behaviour. In addition, suicide is common in people with schizophrenia.

Dysthymia (also referred to as minor depression, neurotic depression or neurasthenia) is a chronic affective disorder distinct from major depression. Recent epidemiological surveys performed in North America and Europe have indicated a lifetime prevalence in the general population of approximately 6% and 4%, respectively. Prevalence rises with age and is higher in women than in men. Dysthymia is associated with comorbidities of major depression, alcoholism, anxiety and personality disorders.

2. Clinical studies

Clinical studies sponsored by the MAH

Four clinical studies have been performed [previously not reviewed by a regulatory authority] whose principal design features are presented in Table 1. Two of the studies (82-00939, 82-00960) were performed in the early 1980s and do not conform to contemporary standards for clinical trials in schizophrenia. Another study was performed with amisulpride in 1989; however the included children were suffering from autism.

The most recent study included both adolescents (15 – 18 years) and adults (18 – 30 years) but did not analyse outcomes separately for the two groups.

Table 1 - Clinical studies of amisulpride in paediatric populations sponsored by the MAH.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>No subjects</th>
<th>Duration</th>
<th>Dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82-00939</td>
<td>Open-label</td>
<td>20</td>
<td>4 weeks</td>
</tr>
<tr>
<td>82-00960</td>
<td>Open-label</td>
<td>16</td>
<td>2 – 64 weeks</td>
</tr>
<tr>
<td>89-00704&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Randomised</td>
<td>9</td>
<td>15 weeks</td>
</tr>
<tr>
<td>95-00734</td>
<td>Randomised</td>
<td>27</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

<sup>1</sup> This study performed in a single centre in France was a randomised, double-blind, crossover trial in nine children with autism, who were severely mentally retarded. This study aimed to compare the clinical efficacy of a dopamine receptor antagonist (amisulpride) with that of a dopamine receptor agonist (bromocriptine) in this population. This study will not be described in detail here as the patients were suffering from autism. This is not an indication for the use of amisulpride.
amisulpride, and this study is considered to be outside the scope of this report, which concerns schizophrenia

**Study 82-00939 (Nissen 1982)**

This was an open-label study performed in a single centre in Germany (Würzburg). The objectives were to evaluate whether amisulpride could favourably affect the gravity of psychotic illness in children and adolescents and to determine the occurrence of undesirable side-effects. Twenty subjects (thirteen boys and seven girls) aged between fourteen and nineteen were included (mean age: 16 years), eighteen of whom had a diagnosis of schizophrenia and two psychosis associated with bipolar disorder. Doses of amisulpride received ranged from 100 to 300 mg/day (1.56 to 6.52 mg/kg/day) and the treatment duration was four weeks. Treatment was discontinued in two patients due to an increase in aggressiveness. Outcome was rated subjectively by the investigator. Two patients were considered to have improved.

**Study 82-00960 (Tridon 1983)**

This was an open-label study performed in a single centre in France (Maxeville). It included a sample of children, all inpatients, with a miscellaneous and poorly-defined variety of behavioural disorders with psychotic features, but none were reported to have a formal diagnosis of schizophrenia. The objective of the study was to evaluate the effects of amisulpride in childhood psychiatric disorders. Sixteen subjects (ten boys and six girls) aged between seven and sixteen were included (mean age: 12 years). Amisulpride was administered as drops at a daily dose of 65 to 400 mg (2-10 mg/day). The treatment duration was variable, ranging from two weeks to sixteen months (mean: five months). Outcome was rated subjectively by the investigator. The treatment response was rated as 'very good' in six cases, 'good' in three cases, 'transient' in three cases and 'poor' in four cases. Patients failing to respond presented neurological syndromes. Treatment was discontinued in one patient due to emergence of side effects (extrapyramidal symptoms).

**Study 95-00734 (Paillère 1995)**

This more recent study used a randomised, double-blind, placebo controlled design and was implemented in four hospital centres in France. The study included 27 patients with significant negative symptoms (defined as a SANS score of ≥55) aged between 15 and 30 years. Eleven patients were under eighteen years of age and sixteen aged between eighteen and thirty inclusive. Patients were not stratified by age group and the data were not analysed separately for the adolescent and young adults groups. Twenty patients were considered evaluable (treated for at least three weeks) and sixteen patients completed the study. The randomisation ratio was 1:1 placebo: amisulpride. Amisulpride was administered at an initial dose of 50 mg/day which could be increased to 100 mg/day at the investigators discretion. Patients were treated for six weeks. The primary efficacy outcome variable was the change in score from baseline in the SANS total score. Total SANS scores decreased by six points (8%) in the placebo group and 24 points (31%) in the amisulpride group (p = 0.056). When individual dimensions of the SANS were considered, significant inter-group differences were observed for the avolition and attention sub-scores in favour of the amisulpride group. No significant inter-group differences were observed for any of the secondary efficacy outcome measures.

**Other Studies**

A literature search of the Medline database was performed by the MAH using 'amisulpride' and 'schizophrenia' as research terms and restricted to studies in children (≤ 18 years of age). This
retrieved 58 items of which only four appeared relevant, all of which were case series or case reports.

**Assessor's comment:** The bibliography section of the worksharing programme provides a total of 74 references many of which are reviews and background material on the management and pharmacological treatment of schizophrenia. Reference numbers 59 to 62 in the Clinical Overview are to the MAH sponsored studies.

**Göpel and Marcus (2001)**

This case series reported the use of amisulpride in ten adolescents aged eight to eighteen years (six boys and four girls) with a diagnosis of schizophrenia or schizoaffective disorder. Seven of the patients were experiencing their first recognised episode of schizophrenia and one had received no previous treatment. Nine patients were switched from another antipsychotic treatment (zuclopenthixol, clozapine, haloperidol or risperidone). Amisulpride was administered at a dose of 250 to 800 mg/day. The authors concluded that their preliminary results on the use of amisulpride were promising and that amisulpride seemed to constitute a useful alternative in the treatment of juvenile schizophrenia for patients who suffered from intolerable side effects of classical or atypical antipsychotics. Eight patients were considered to be greatly improved, and two patients improved following initiation of amisulpride treatment. However, they cautioned that controlled studies would be warranted to establish the efficacy and safety of amisulpride in the treatment of adolescents.

**Assessor's comment** – the paper is in German with an English abstract so lacking in detail as to be meaningless – the MAH’s summary of the paper, above, is much more informative.

**Bohne et al. (2003)**

This case series evaluated three boys and four girls with first-episode schizophrenia or schizoaffective disorder (mean age 15.4 years) who were treated with amisulpride in combination with another antipsychotic (levomepromazine, risperidone or haloperidol) for 32 days. Outcome was assessed with the BPRS and the PANSS. In three patients, the mean BPRS score decreased from 63 points to 30, the PANSS positive symptoms score from 25 to 9 and the PANSS negative symptoms score from 19 to 13, following initiation of amisulpride. Quantitative outcomes were not reported for the other patients, who presumably did not respond to treatment. The authors concluded that amisulpride could be a promising treatment for schizophrenia in adolescents, with a favourable risk-benefit ratio.

**Assessor’s comment.** The reference is an abstract (in German) of a presentation at Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Berlin, Germany, 19-22 November 2003. -- Nervenarzt, 2003, 74(Suppl. 2), p. S305

**Murphy (2003)**

This case report described a seventeen-year old girl with a four-year history of schizophrenia presenting with persistent negative symptoms, who was switched, in light of her syndrome presentation, from olanzapine to amisulpride (400 mg/day) and was treated throughout with citalopram. Following switching, her negative symptoms, as assessed with the SANS, improved rapidly. However, her mood rose concomitantly and by three months she presented a non
psychotic manic episode. The manic episode faded when the dose of amisulpride was halved and resolved completely after switching back to olanzapine.

**Assessor’s comment:**
The publication is a letter to Br. J. Psychiatry, 2003, 183(2):172 and is accurately reflected in the description above.

*Bailly et al. (2004)*

This was a case report of an unusual case of very-early onset schizophrenia concerning a young girl with multiple familial antecedents of schizophrenia who developed a typical clinical picture of paranoid schizophrenia by age nine. Following an inadequate therapeutic response to haloperidol (recurrence of a psychotic episode), she was switched to treatment with amisulpride (600 mg/day). No clinical benefit was observed and she was started on clozapine, which led to a clinically significant reduction in hallucinations and disorganized behaviour.

**Assessor’s comment.** The paper (L’Encéphale, 2004; XXX:540-7, cahier 1) is in French with a long English summary which is consistent with the description provided above.

**Assessor’s comment.** There is an additional paper among the 74 references provided (Varol Tras F., Guvenir T., Amisulpride treatment of adolescent patients with schizophrenia or schizoaffective disorders; Eur Child Adolesc Psychiatry 2009 18:511–513) which describes three female adolescents (aged 15, 16, 17) treated with amisulpride at an inpatient facility all of whom had a response to treatment and all of whom developed hyperprolactinaemia and galactorrhea. It is unclear why this paper is not reviewed as it seems as relevant as the four references which were reviewed (above).

**OVERVIEW OF SAFETY**

MAH Sponsored clinical studies

Study 82-00939; 20 twenty patients; tolerance was described as “very good” in 2 cases and as “good” in 18. Side-effects; increasing psychomotor disturbance (verbal and physical attacks on people and things) were found in two cases, and in both, therapy was discontinued.

Study 82-00960; 16 sixteen patients three young patients presented neurological effects after 2 months of treatment; tremor, facial dystonia, buccopharyngeal dystonia. Therapy was discontinued in the third case due to lack of efficacy.

Study 89-00704; 9 patients. No safety data were reported.

Study 95-00734 27; 12 patients receiving amisulpride and 5 receiving placebo had extrapyramidal symptoms rated “very mild” on their last assessment. Insomnia, excitement, or somnolence was reported by 8 patients taking amisulpride and by 5 taking placebo

In the study of Bohne S et al. (Klinische Beobachtungen zur Psychopharmakotherapie der Schizophrenie im Jugendalter in besonderem Hinblick auf Amisulprid. Nervenarzt 2003;74(Suppl 2):S305) Six adolescents showed extrapyramidal side effects prolactin rose in all cases and caused clinical symptoms in one patient.

**MAH database.**
The Sanofi pharmacovigilance database was searched for worldwide medically-confirmed and non-medically-confirmed unsolicited cases in paediatric patients aged from 12 to 17 years (or with an age group captured in the database as adolescent) exposed to amisulpride and reported up to 30 June 2012.

One hundred and forty-two cases involving a patient between 12 to 17 years of age were recorded. The majority (133) were medically confirmed. The country with the most cases reported (52) was France. Among the 142 cases, 49 were serious and 93 non-serious. Seventy-seven cases concerned a female and 59 a male patient (gender was not specified in 6 cases).

The most significant adverse reactions due to their frequency or their severity are detailed below.

- **Hyperprolactinemia**
  Hyperprolactinemia and/or related symptoms (blood prolactin increased, galactorrhoea, gynaecomastia, breast pain, breast enlargement, and amenorrhoea) were reported in 45 cases (and 69 adverse reactions).

- **Extrapyramidal symptoms**
  Extrapyramidal symptoms (parkinsonism, tremor, akathisia, dyskinesia, salivary hypersecretion) were reported in 25 cases (and 32 adverse reactions). Among these adverse reactions, 15 resolved, 2 were resolving and 1 was not resolved at the time of reporting (the outcome was not reported in 12 reactions).

- **Dystonia**
  Dystonia and related symptoms (oculogyric crisis, muscle spasms, oropharyngeal spasm) were reported in 16 cases (and 18 adverse reactions).

- **Weight increase**
  Weight increase was reported in 13 cases. The average weight increase was of 8.9 kg in the 9 cases where this value was reported.

- **Tardive dyskinesia**
  Four cases of tardive dyskinesia were reported. In one case the dyskinesia improved, Abnormal Involuntary Movement Scale [AIMS] score dropped from 8 to 3, two months after amisulpride dose reduction (from 600 mg to 400 mg daily) but had not resolved one year later (2010SA035444, 72). In one case, the reaction persisted 2 weeks after amisulpride and risperidone withdrawal whereas cyamemazine had been maintained (A02200902540). In one case the dyskinesia recovered within one week after treatment discontinuation (A02200603269). In the last case the outcome was not reported (A01200600468).

- **Neuroleptic malignant syndrome**
  Two cases (A04200700764 and S/FRAMI00002) of neuroleptic malignant syndrome were reported. Both adolescents recovered within a few days.

- **QT prolongation and related disorders**
  QT prolongation and related disorders, ie: electrocardiogram QT prolonged (n = 7) and torsade de pointe (n = 1, A01200303418) were reported in 8 cases. A01200303418: A 16-year-old female patient with a medical history of lamotrigine hypersensitivity experienced febrile itchy rash about one month after starting amisulpride 100 mg/d (for personality paranoid disorder) and 2 weeks after starting oxcarbazepine 600 mg (for
epilepsy). The same day, ECG revealed torsade de pointes. Oxcarbazepine and amisulpride were stopped, leading to complete recovery within 3 days.

- Consciousness disorders
  Consciousness disorders (coma n = 1, depressed level of consciousness n = 1, sedation n = 3, and somnolence n = 3) were reported in 8 cases.

Reports of use in a context of overdose

Amisulpride was considered to be taken in overdose when it was reported as such or when the daily dose was higher than 10 mg/kg or higher than 1200 mg (maximum daily dose in adults). In three cases overdose was reported, two with suicidal intent and one undetermined; all three patients recovered rapidly without sequelae. In seven cases amisulpride daily dose was higher than 10 mg/kg, however no overdose was reported in these cases.

Fatal cases

There were two reports of adverse events with fatal outcome.

Case S/FRAI96101: A 17-year-old female patient hospitalised in a psychiatric unit was treated with amisulpride 400 mg/day, clorazepate 150 mg/day, amitriptyline 100 mg/day, levomepromazine 75 mg/day, and trihexyphenidyl 4 mg/day for an unspecified psychiatric disorder. An unspecified time later, she was found dead in her bath. Concentrations in blood samples taken post-mortem of amisulpride (530 ng/ml), amitriptyline, levomepromazine, and nordiazepam were in the therapeutic range.

Case A02200901883: A 17-year-old male patient with a medical history of psychiatric disorder since the age of 14 year old was hospitalised for catatonic state and dissociative disorder. On admission, Electrocardiogram was unremarkable. He was treated with hydroxyzin, cyamemazine, and loxapine. One day later, he was started on amisulpride (400 mg daily) and cyamemazine by injectable route. Two days later, the patient received amisulpride (100 mg) and cyameemazine (25 mg) via the intramuscular route. A few hours later, tropatepine (5 mg) was administered via intramuscular route for acute dystonia. Ten minutes later, the patient experienced cardio-respiratory arrest. He was treated with cardiac massage, adrenaline, and intubation. He experienced tachycardia and fever at 38° Celsius. Electrocardiogram showed a long QT interval. Laboratory workup revealed signs of tissue hypoinfusion with lactates at 8 mmol/L, hepatic cytolysis (transaminases at 1300 IU/L), and Creatine Phosphokinase (CPK) increased. Echocardiography (except for tachycardia), thoracic and brain CT-scan were unremarkable. Six days later, the patient was in a state of brain death. Toxicological workup revealed cyamemazine at 0.023 mg/L (normal therapeutic value: 0.05-0.4 mg/L) and amisulpride at 0.305 mg/L (normal therapeutic value: 0.03-0.12 mg/L). Autopsy results were negative. No clear-cut etiology was found for cardio-respiratory arrest (cardiac organic origin, brain haemorrhage and thrombophlebitis, and pulmonary embolism were excluded).

Assessor’s comment:
The MAH makes the following evaluation of the two fatal cases which the assessor endorses “Both adolescents were treated with two antipsychotic drugs and their blood values for amisulpride were above therapeutic range. In both cases a cardiac rhythm disorder may be suspected.” From the case narratives each patient seems to have received four antipsychotic medications, though the degree of overlap is not assessable. The requirement for this degree of co-medication is a clinical and not a regulatory decision.
3. Discussion on clinical aspects

The MAH has provided a comprehensive and well-written review of the use of Solian (amisulpride) in children and adolescents. Use of amisulpride in pre-pubertal children seems to be minimal. It is likely that some of the patients at the lower end of the age range in some of the studies cited were pre-pubertal but this is likely to be limited to tens of children.

Seventy-two children and adolescents were treated in company-sponsored studies and 142 adolescents (aged 12 to 17 years) were identified in the company database. A minor criticism of the review is that the database search was limited to those aged 12 years and over on the grounds that Solian is contradicted in pre-pubertal children.

With regard to clinical benefit, the four company-sponsored trials were small, conducted from 1982 – 1995 and the earlier studies appear to have been conducted in a population of autistic children and some with organic brain syndromes, in many/the majority the diagnosis of schizophrenia is very insecure. Collectively, the company sponsored studies are incapable of answering whether amisulpride may, or may not, have clinical benefit in post-pubertal adolescent patients with schizophrenia. Unfortunately, the same comments apply to the existing published literature.

The safety profile of amisulpride in adolescents appears consistent with that in adults and with the current SmPC. An exception may be the occurrence of two fatal events in a database of just over 200 patients. However, the degree of co-medication seems likely to be a contributory factor; the justification for that cannot be evaluated on the available data and is a matter of clinical judgment outside the regulatory remit.

IV. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The MAH has provided a review of the use of amisulpride in children and adolescents which is of good quality and appears comprehensive. The available data are inadequate to make an evaluation of clinical benefit, if any. The safety profile is consistent with that in adults and is appropriately described in the product information.

➢ Recommendation

No further action required.

V. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The review was provided solely by Sanof-Aventis therefore the data pertaining to company-sponsored studies and the pharmacovigilance data are specific to Solian. However, searches of publically accessible databases using the active substance term “amisulpride” were also conducted so the results pertain to the active substance and to the trade name.