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

Haloperidol

FR/W/011/pdWS/001

Rapporteur:	FR
Finalisation procedure (day 120):	31 January 2012
Date of finalisation of PAR	February 2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	haloperidol
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	Antipsychotics – group of the butyrophenones N05AD01
Pharmaceutical form(s) and strength(s):	See section VIII

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LIST OF ABBREVIATIONS

AD	Autistic Disorder
ADHD	Attention deficit hyperactivity disorder
AP	Antipsychotic
BID	Bis in die
CCDS	Company Core Data Sheet
DSM	Diagnostic and statistical Manual of mental disorder
EPS	Extrapyramidal Symptoms
EU	European Union
GTS	Gilles de la Tourette syndrome
HS	Hours of sleep
IV	Intra-venous
J&J PRD	Johnson &Johnson Pharmaceutical Research and Development
MAH	Marketing Authorisation Holder
PDD	Pervasive Developmental Disorder
PL	Packet Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristic
TD	Tic Disorder
TID	Ter in die
TS	Tourette syndrome
Y	Years

I. EXECUTIVE SUMMARY

On the preliminary assessment report, no recommendation on use in schizophrenia and Gilles de la Tourette's disorder in children and adolescents could be made because of the lack of sufficient data on efficacy and the safety profile of haloperidol.
A global analysis on the use of haloperidol as psychomotor anti-agitation agent in children with conduct disorder or pervasive developmental disorders was requested to the MAH.

Haloperidol seems to be efficacious, with careful dose administration, for treating several of the behavioural symptoms associated with autism, as withdrawal, stereotypy, irritability and hyperactivity.
However, the current dossier provided by the MAH did not permit to well define the aimed symptoms, the paediatric population (diagnosis and age range) who may benefit from haloperidol treatment and the posology.
Furthermore, this efficacy must be balanced against the important adverse effects (i.e. Extrapyramidal symptom, neuroleptic malignant syndrome, and sedation).

II. RECOMMENDATION

On the basis of the submitted data, with rather old studies, no formal recommendation on indications could be made.
However, it is not the aim of the paediatric worksharing procedure to remove paediatric indication.
We suggest that haloperidol could be included on the list of the future SPC harmonisation and that this review could be performed via an appropriate regulatory procedure.

The Rapporteur recommends changing the SmPC as follows:

4.4 Special Warnings and Special Precautions for Use

~~None~~
Available safety data in the paediatric population indicate a risk of extrapyramidal symptoms, including tardive dyskinesia, and sedation. No long-term safety data are available.

In line with these changes, the corresponding sections of the PIL should be updated as follows:

2. What you need to know before you <take> <use> X
Warnings and precautions
Available safety data in the paediatric population indicate a risk of extrapyramidal symptoms, including tardive dyskinesia (involuntary, repetitive body movements), and sedation. No long-term safety data are available.

MAHs are thus requested to submit type IB variations to update the Product Information of haloperidol-containing medicinal products accordingly.

III. INTRODUCTION

Haloperidol is a potent central dopamine receptor antagonist belonging to the group of the butyrophenones neuroleptics. Haloperidol has virtually no antihistaminergic or anticholinergic activity. Haloperidol is marketed, in most countries, under the trade name HALDOL®. The long acting formulation is haloperidol decanoate, which is a solution for intramuscular injection. Haloperidol decanoate is intended for use in chronic psychotic patients who require chronic therapy.

The first approval of haloperidol was in Denmark in July 1959. Currently, haloperidol is licensed in 105 countries around the world. Haloperidol formulations are registered in the EU in Austria, Belgium, Luxembourg, Cyprus, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Malta, Netherlands, Portugal, Romania, Spain, Sweden and the UK.
According to information from the SmPCs in EU submitted by the MAH, haloperidol seems to be used:

- "As psychomotor anti-agitation agent: disorders of behaviour and character in children, especially when associated with hyperactivity and aggression and particularly in the context of autistic syndromes" in 10 Member States
- "In Gilles de la Tourette's disorder" in 6 Member States
- "In Psychoses, including childhood schizophrenia" in 5 Member States
- "In Chorea" in 1 Member State
- "In post-operative nausea and vomiting" in 1 Member State

In FI, EL, NL, HU and ES, a recommended dosage in children is available into section 4.2.
No indications in children in 2 Member States.

The MAHsubmitted 49 completed paediatric studies for haloperidol, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.
A literature summary and evaluation of haloperidol use in children has been provided. This summary discussed about the 49 completed paediatric studies (dated from 1967 to 2009).

In addition, the following documentation has been included as per the procedural guidance:

- A bibliographic list
- The Company Core Data Sheet (4 December 2009) in which indications are listed without regard whether they are applicable to children or adults

No quality and non-clinical published information have been submitted.

Information available into the CCDS concerning paediatric population is:

4.1 Therapeutic indications:
As a psychomotor anti-agitation agent in:

- Disorders of behaviors and character in children

4.2 Posology and method of administration:
In children: 0.1 mg/3 kg body weight TID orally, may be adjusted if needed.

The MAH stated that the submitted paediatric studies do no recommend any changes to the paediatric indication already registered in the EU but does propose the following amendment to the posology section of the SmPC/PL without justification:

“Treatment should start with 0.025-0.033 mg/kg weight orally three times a day and should be adjusted as necessary. The maximum recommended daily dosage is 0.28 mg/kg/d, based on dosages studied in clinical trials of haloperidol in children”.

The MAH claimed that the clinical study data presented and reviewed here are supportive of the following indications in paediatrics as found in the various SmPCs throughout the EU:

- As psychomotor anti-agitation agent: childhood behavioural disorders, especially when associated with hyperactivity and aggression and serious behaviour disorders (agitation, self injury, stereotypic movement disorder) particularly in the context of autistic syndromes
- Psychoses in children, including childhood schizophrenia
- Gilles de la Tourette’s disorder

The 49 submitted studies provided from the MAH cumulative search, are considered by the MAH as the best-available pharmacodynamic, pharmacokinetic, efficacy and safety trials of haloperidol in children identified. However, the MAH did not provide a global analysis of the clinical data available, only a descriptive review of each publication.

IV. PRELIMINARY SCIENTIFIC DISCUSSION

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

The registered formulations, worldwide, of haloperidol are tablets containing 1, 2, 5, 10 and 20 mg of haloperidol, oral solution containing 2 mg and 10 mg haloperidol per ml and injectable solution containing 5 mg haloperidol per ml.
The formulations for injection are only used in adults.
From the brief documentation provided by the MAH, the pharmaceutical formulations used are not explicitly stated, excepted into the section 5.9 “IV use in critically ill children with agitation and delirium”.

IV.2 Non-clinical aspects

No non-clinical documentation was provided.

IV.3 Clinical aspects

1 Introduction

A list of all the clinical studies submitted is included (see line-listing provided by the MAH in Section VIII).

The MAH submitted 49 publications (1967-2009).
The MAH did not submit reports or extended synopsis.

The MAH provided publications on haloperidol use in children with schizophrenia, Tourette’s disorder and tic disorder, in the treatment of autistic disorder and atypical pervasive developmental disorders, in aggressiveness, in ADHD, in anxiety-tension states, in emotionally disturbed children with heterogeneous diagnoses, in delirium and intravenous use in critically ill children with agitation and delirium.

2 Results on pharmacodynamics in children

The MAH provided the two following publications (Wudarsky, 1999 and Sallee, 1996):

First author	Product/ Indication	Mean; Mg/kg/d; Maximum dosage	Comparator	Report type	No. of patients haloperidol/ total (age range)	Results
Wudarsky M.[2]	Haloperidol/ Schizophrenia	15.3±8.23 mg/d; 0.27 mg/kg/d	Clozapine/ Olanzapine	Open or double-blind active controlled	10/ 35 (9-19y)	Mean prolactin levels were significantly elevated for all groups after 6-week treatments, with olanzapine and haloperidol above the upper limit of normal.
Sallee FR.[3]	Haloperidol/ Tourette's disorder	3.5+-2.2mg/d	Pimozide/ Placebo	Double-blind placebo controlled	26 (7-16y)	Clinical response rates of 69% on 3.4 +/- 1.6 mg pimozide and 65% on 3.5 +/- 2.2 mg/day haloperidol. Prolactin may be a marker for tic response to pimozide, and conversely, a potential marker for haloperidol-related incidence of extrapyramidal symptoms during haloperidol therapy

Wudarsky[2] (1999) compared serum prolactin measured in children and adolescents treated with typical and atypical antipsychotics, to published data for adults. Children and adolescents, aged 9 to 19 years (mean age, 14.1 ± 2.3 years) diagnosed with childhood onset schizophrenia or Psychotic Disorder not otherwise specified with onset of psychosis before their 13th birthday, were recruited into 6-week, open or double-blind trials of haloperidol (n=10), clozapine (n=15), or olanzapine (n=10). At week 6 the mean dose of haloperidol was 15.3±8.23 mg/d (0.27 mg/kg), olanzapine 17.0±3.5 mg/d and clozapine 325.4±211.0 mg/d. Mean prolactin concentration after 6 weeks of treatment was significantly elevated on all three drugs; however, on clozapine, mean prolactin remained within the normal range. Prolactin was increased above the upper limit of normal for 100% of 10 patients on haloperidol, 70% of 10 patients on olanzapine, and 0% of 15 patients on clozapine.

The authors concluded that these pilot data suggest that youths may have a more robust prolactin increase than do adults to typical and at least to some atypical antipsychotics. They cited publications in which it is stated that antipsychotic-induced prolactin elevations are associated with menstrual disturbances with 15-50% prevalence; with galactorrhea with a 10-50% incidence, and with impotence and azospermia in men. Additionally, elevated prolactin can inhibit gonadotropinreleasing hormone secretion, which can then disrupt lutenizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. Decreased peaks of LH and FSH can result in insufficient ovarian production of estrogen. The end result of this cascade, hypoestrogenemia, might increase the risk of cardiovascular disease in women. The risk hyperprolactinemia poses to women's cardiovascular health has not yet been established by controlled studies. The authors stated tha because the prolactin concentrations are below the value range associated with hyperprolactinemic-induced physiological disturbances (amenorrhea usually occurs with prolactin above 60-100 ng/ml), these findings may not be of clinical concern. These findings are limited by the small sample size, limited duration of observation, and lack of direct comparison with adult data from similar trial design.

Assessor's comments:
Antipsychotic drugs are thought to disinhibit prolactin secretion by D_2 receptor blockade.
In children and adolescent, hyperprolactinemia can result in galactorrhea, amenorrhea, gynecomastia, and maturational delay as stated by Rosenbloom (2010).
In his review, Rosenbloom (2010)[a] mentioned antipsychotics, particularly haloperidol and risperidone, to be associated with the greatest risk of hyperprolactinemia. He concluded that, in addition to monitoring for signs and symptoms of hyperprolactinemia in children and adolescents taking AP medications, monitoring serum prolactin concentrations is warranted. And, that in the presence of hyperprolactinemia, cessation of AP therapy or changing to a formulation less likely to raise prolactin levels should be considered.
We agree that hyperprolactinemia with antipsychotic drugs is a well-known concern, especially in paediatric population and should be well-informed into the CCDS and the SmPC into sections 4.4 and 4.8.

Sallee[3] (1996) examined if one could assess the potential outcome in Gilles de la Tourette's syndrome (GTS) from a physiologic marker such as plasma prolactin concentration. In a double-blind, placebo-controlled, double crossover comparison of pimozide and haloperidol therapy, prolactin, tic severity, and extrapyramidal symptoms were assessed at a 6-week end point. Mean treatment doses of pimozide (3.4 ± 1.6 mg/d) and haloperidol (3.5 ± 2.2 mg/d) were equivalent. Twenty-six GTS patients (10.5 ± 2.6 years), experienced clinical response rates (≤50% reduction in Tourette Syndrome Global Scale from baseline) of 69% on 3.4 ± 1.6 mg pimozide and 65% on 3.5 ± 2.2 mg/day haloperidol. Pimozide responders demonstrate elevated prolactin (26.1 ± 11.8 ng/ml) versus pimozide nonresponders (10.5 ± 3.8 ng/ml) (p = 0.05) and haloperidol treated patients (p = 0.05). (see Table 1, results at 6 weeks)

Table 1. Treatment Outcome: Crossover Comparison of Placebo, Pimozide, and Haloperidol

	Mean (±SD)		
Outcome measure	Placebo	Pimozide	Haloperidol
Prolactin (ng/mL)	6.8 (2.5)	21.6 (19.5)[a]	12.9 (8.4)[a]
TSGS (total)	26.7 (15.7)	15.2 (12.8)[b]	19.6 (17.7)
CGI	4.6 (1.0)	3.1 (1.4)[a]	3.1 (1.4)[a]
ESRS	1.4 (3.0)	2.0 (3.0)	4.1 (6.9)[a,c]
AIMS	0.2 (0.7)	0.4 (1.1)	0.3 (1.1)

[a] $p < .01$ compared to placebo.
[b] $p < .05$ compared to placebo.
[c] $p < .05$ compared to pimozide.

TSGS: Tourette Syndrome Global Scale
CGI: Clinical Global Impression Tic Severity scale
ESRS: Extrapyramidal Symptoms Rating Scale
AIMS: Abnormal Involuntary Movement Scale

Responders to haloperidol differed little from nonresponders with regard to plasma prolactin concentration (13.4 ± 9.3 ng/ml vs. 12.2 ± 7. 4 ng/ml, respectively).
For haloperidol, EPS was not dose related but best associated with plasma prolactin concentration (PRC) elevation (Table 2). Patients treated with haloperidol who exhibited EPS (PRC = 17.8 ± 10.3) at week 6 differed from those without EPS (PRC = 8.8 ± 4.6) in prolactin concentration (p = 0.04).

[a] Rosenbloom AL. Hyperprolactinemia with antipsychotic drugs in children and adolescents. Int J Pediatr Endocrinol. 2010;2010.pii:159402.Epub 2010 Aug 24.

Table 2. Prolactin Levels Associated with Clinical Response and Extrapyramidal Symptoms (EPS)

	Mean ± (SD)			
	Responder		Nonresponder	
Treatment	No EPS	EPS	No EPS	EPS
Haloperidol	10.1 (5.7) (n = 7)	17.4 (11.9) (n = 5)	7.8 (1.6) (n = 4)	15.5 (8.6) (n = 3)
Pimozide	20.7 (15.1) (n = 9)	33.7 (26.9) (n = 8)	10.4 (4.7) (n = 5)	10.8 (2.8) (n = 3)

The authors concluded that for the haloperidol treatment condition, plasma prolactin concentration appeared to be related to EPS and that the present findings would suggest that low PRC (≤ 10 ng/ml) is associated with absence of EPS in 90% of haloperidol-treated children and adolescents with GTS. This suggests that PRL may be an efficient marker and an additional means to avoiding EPS during haloperidol therapy.

Assessor's comments:
EPS are well-known undesirable effects of haloperidol which should be added into section 4.4 as a warning and 4.8. The MAH should precise if EPS frequency and nature in children and adolescents differs from those observed in adults.

3 Results on pharmakinetics in children

As stated in the CCDS:

Absorption
Following oral administration, the bioavailability of the drug is 60 to 70%. Peak plasma levels of haloperidol occur within two to six hours of oral dosing and about twenty minutes after intramuscular administration.

Distribution
Plasma protein binding is 92%. The volume of distribution at steady state (VDss) is large (7.9±2.5 L/kg). Haloperidol crosses the blood-brain barrier easily.

Metabolism
Haloperidol is metabolized by several routes including the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6) and glucuronidation.

Elimination
The mean plasma half-life (terminal elimination) is 24 hours (range 12 to 38 hours) after oral administration and 21 hours (range 13 to 36 hours) after intramuscular administration. Excretion occurs with the faeces (60%) and the urine (40%). About 1% of the ingested haloperidol is excreted unchanged with the urine.

Therapeutic Concentrations
It has been suggested that a plasma haloperidol concentration range from 4 µg/l to an upper limit of 20 to 25 µg/l is required for a therapeutic response.

The MAH provided 3 publications on pharmacokinetic of haloperidol in children.

First author	Product/ Indication	Mean; Mg/kg/d; Maximum dosage	Comparator	Report type	No. of patients haloperidol/ total (age range)	Results
Morselli PM.[4]	Haloperidol/ Psychotic episodes, tics, and stuttering	0,015-0,285 mg/kg/day		Observational study	23 (7-20y)	Steady-state haloperidol plasma levels in children may vary up to 15 - fold at a given mg/kg daily dosage. Side effects too appeared to be related to plasma levels, with a significant increase ($p < 0.01$) in incidence for concentrations over 6 ng/ml.
Morselli PM[5]	Haloperidol/ Psychosis			Observational study		In the two children who were investigated, who had slightly reduced albumin but increased α-acid glycoprotein concentrations, the free fraction of haloperidol appeared to be reduced (7.3 and 7.9 percent)
Morselli PM[6]	Haloperidol/ Neuropsychiatric conditions			Review		In general, children require lower plasma levels for the same therapeutic effects. A clear correlation appears to exist between plasma concentrations and side effects or adverse reactions

Morselli[4] (1979) observed 23 children of 7-20 years of age who were suffering from either psychotic disturbances and/or severe abnormal movements (tics and Gilles de la Tourette's syndromes) for periods varying from 1 to 10 months. The parameters monitored were the clinical picture, the presence of adverse toxic effects, and the plasma levels of haloperidol.
Haloperidol was administered at doses ranging from 0.015 to 0.285 mg/kg/day, associated with anticholinergic treatment in 20 cases. Haloperidol was administrated alone in 2 cases.
Steady-state concentrations of haloperidol ranged from 0.7 to 19 ng/ml without any apparent relationship with the administered dose and a 6-15-fold variability was observed for the same daily dosage. On the contrary, a significant ($p < 0.02$) relationship was found between the age of the patients and the plasma concentrations to dose ratios, lower values being present in

younger patients. Side effects too appeared to be related to plasma levels, with a significant increase ($p < 0.01$) in incidence for concentrations over 6 ng/ml.
Practically, for plasma levels below 6 ng/ml, less than 20% of the patients suffered from adverse reactions such as drowsiness, sleepiness, extrapyramidal syndromes, blurred vision, dystonic reactions, etc., while for levels between 6 and 9 ng/ml, these side effects were present in 75% of the cases. For plasma levels over 10 ng/ml, adverse effects were present in 90% of the cases and were very intense. In most of the cases suffering from tics and Gilles de la Tourette's syndrome, a positive response was associated with plasma levels of 1-4 ng/ml, while no relationship could be established for the psychotic group. The authors concluded that in children, as well as in adults, there is an important inter-individual variability in haloperidol plasma concentrations, that there is an important age effect on the disposition of the drug, and, more importantly, that the incidence of adverse effects is significantly correlated to the drug concentrations in plasma.

Morselli[5] (1981) investigated serum protein binding of haloperidol in healthy volunteers, elderly subjects, cirrhotic patients and psychotic children. The studies were all carried out *in vitro* using equilibrium dialysis at 37°C with 3H-labeled haloperidol. These observations were part of a larger program aimed at evaluating the influence of age and different pathological conditions on the clinical pharmacokinetics of haloperidol and the relationship between possible changes in pharmacokinetics and clinical response. Results showed that in the group of healthy volunteers the mean unbound fraction of haloperidol was 11.6 percent with only a small inter-individual variation (10-13 percent). In elderly subjects who showed reduced albumin but increased α-acid glycoprotein (AAG) concentrations, the free fraction of haloperidol was significantly reduced (mean 8.5 percent, range 6.6-9.6 percent). On the other hand, for cirrhotic patients, who had both reduced albumin and reduced AAG concentrations, the free fraction of haloperidol was significantly increased compared to both healthy volunteers and elderly patients (mean 18.9 percent, range 12.4-23.6 percent). In other hepatically impaired patients with normal or elevated AAG concentrations (>0.6 g l-1), the free fraction of haloperidol was only moderately increased (mean 13.1 percent). In the two children who were investigated, who had slightly reduced albumin but increased AAG concentrations, the free fraction of haloperidol appeared to be reduced (7.3 and 7.9 percent). The authors concluded that, both age and concurrent disease states may have an influence in determining individual differences in haloperidol binding. Part of this variability may be mediated by AAG but other serum proteins may also be involved. In some patients treated with haloperidol the unbound concentration of drug may be more important in determining clinical effects than total (bound+unbound) plasma concentrations.

Morselli[6] (1982) later reviewed the data earlier referenced above regarding haloperidol pharmacokinetics and haloperidol plasma concentration monitoring in neuropsychiatric patients. The authors concluded that in general, children required lower plasma levels for the same therapeutic effects. A clear correlation appeared to exist between plasma concentrations and side effects or adverse reactions.

Assessor's comments:
Data confirm that there is an important inter-individual variability in haloperidol plasma concentrations, that there is an important age effect on the disposition of the drug, and that the incidence of adverse effects is significantly correlated to the drug concentrations in plasma. Furthermore, children required lower plasma levels for the same therapeutic effects than adults.
It seems important to detail into section 4.2 the dosage schedule for children and adolescents with a low initial dose and progressive increment of the dose based on benefit and tolerability.

4 Drug-drug interactions

There were no clinical trials retrieved on drug-drug interactions in children.

5 Efficacy

5.1 Use in schizophrenia

The MAH provided 7 publications on use of haloperidol in paediatric population with schizophrenia. Two publications were double-blind, placebo-controlled studies, 3 were double-blind, active-comparator-controlled studies, and 2 were open-label, active-comparator-controlled studies. (See tables below)

Double-blind, placebo-controlled studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl (M/F)	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Pool D.[7] 1976	Efficacy of LXP in adolescents with schizophrenia	DB, RD, vs PLA and LXP,	4 weeks	75 HAL: 18/25 LXP: 10/26 PLA: 15/24	HAL: 15.7 y LXP: 15.6 y PLA: 15.3 y	Average LXP: 87.5mg/d HAL: 9.8mg/d	13/18 years, schizophrenia with thought associations and/or hallucinations	BPRS NOSIES CGI
Spencer E.[8] 1992	Safety and efficacy of HAL in hospitalized schizophrenic children	DB, RD, cross-over vs PLA	8 weeks	12 (9/3)	8.78 y (5.5 to 11.75 y)	0.5 – 3.5 mg/d (0.02-0.12 mg/kg/d)	Schizophrenia by DSM-III-R criteria	Staff Global Clinical Judgments

DB: double-blind; RD: randomised, PLA: placebo; HAL: haloperidol; LXP: loxapine
BPRS: Brief Psychiatric Rating Scale; NOSIES: Nurses' Observation Scale for Inpatient Evaluation; CGI: Clinical Global Improvement.

Pool[7] (1996) evaluated the efficacy of loxapine succinate as compared to haloperidol and placebo in 75 adolescents (13-18 y) with schizophrenia in a 4-week double-blind, randomised study. The haloperidol dosage schedule was as follows: 2 mg h.s. for day one and two, 2 mg b.i.d. for day three, 2 mg, 3 times daily for days 4 to 7, and 2 mg, 5 times daily for days 8 through 10. Average daily dosage was 87.5 mg for loxapine and 9.8 mg for haloperidol.
Results indicated that on the BPRS ratings, there were significant changes from baseline in all three treatment group, on all items. The BPRS showed no significant differences between the two active drug groups. The NOSIE failed to show overall significant improvement.
On the CGI scale, *Treatment Comparisons* as evaluated by the covariance analysis comparing global impressions at each rating time showed that there were no significant differences among the treatment groups. The proportion of patients "improved" or "not improved" in the three groups showed similar results. However, for patients who were rated "severely ill" or "very severely ill" at baseline, there was a trend (p=0.06) at week *four* showing a larger portion of patients "improved" in the two active drug groups (87.5% for loxapine, 70% for haloperidol) as compared with the placebo group (36.4%).
The most common side effects noted were extrapyramidal side effects in 19 of the 26 subjects receiving loxapine and 18 of the 25 subjects receiving haloperidol. The second most common side effect was sedation which occurred in 21 of the loxapine subjects and 13 of the haloperidol subjects.

Spencer[8] (1992) presented preliminary findings in an ongoing double-blind, placebo-controlled study (still ongoing at the publication's date) of the safety and efficacy of haloperidol in 12 hospitalized schizophrenic children aged 5.5 to 11.75 years.

This 10-week study employed a crossover design. After a 2-week placebo baseline period, subjects entered 8 weeks of double-blind treatment, by random assignment receiving either haloperidol for 4 weeks followed by placebo for 4 weeks, or alternatively, placebo for 4 weeks followed by haloperidol for 4 weeks. Dosage began with 0.5 mg/day. Optimal haloperidol dose ranged from 0.5 to 3.5 mg/day (0.02-0.12 mg/kg/day), with mean optimal haloperidol dose 2.02 mg/day. For 8 of 12 subjects, optimal dose was 0.04 to 0.06 mg/kg/day. The 2 subjects requiring the highest doses for optimal response were sisters, who received 3.0 and 3.5 mg/day, respectively (0.11 and 0.12 mg/kg/d).

According to staff Global Clinical Judgments comparing each of the two double-blind treatments to baseline, all 12 subjects on haloperidol showed improvement: marked in 9, moderate in 2, and mild in 1. On placebo, compared with baseline, 10 showed mild improvement, 1 showed mild worsening, and 1 showed moderate improvement.

TABLE 1. Haloperidol Treatment Effect: Mean Clinical Global Impressions (CGI) Ratings for 12 Schizophrenic Children.

CGI Item	Baseline	Placebo	Haloperidol
#1, Severity	5.15	4.33	2.99***
#2, Improvement	3.58[a]	2.58	1.54*

*$p < .05$, one-tailed.
***$p < .001$, one-tailed.
[a]Baseline improvement = change between first and second placebo baseline ratings.

TABLE 2. Haloperidol Treatment Effect: Mean Scores for 8 Children's Psychiatric Rating Scale (CPRS) Items in 12 Schizophrenic Children.

	Mean CPRS Ratings		
CPRS Item	Baseline	Placebo	Halo-peridol
#17 Suspicious Affect	2.33	1.68	1.25
#19 Blunted Affect	2.37	2.76	2.26
#57 Ideas of Reference	2.09	2.03	1.31*
#58 Persecutory	3.06	2.68	1.31**
#59 Other Thinking Disorders	3.48	2.89	2.11*
#61 Hallucinations	4.25	3.46	1.97*
#60 Delusions	4.16	3.33	2.61
#62 Peculiar Fantasies	3.44	2.73	2.56

*$p <$ one-tailed.
**$p = .01$, one-tailed.

Side effects associated with haloperidol were drowsiness (8), drooling (4), dizziness (2), tongue discomfort (2), acute dystonic reaction (3 or 2, discrepancies between table and text) and mask-like facies (1), cogwheel rigidity of arm (1), decreased arm-swing while walking (1), mild tic-like lip movements (1), minimal vermicular tongue movements (1). They resolved either during dosage maintenance or with dosage reduction.

Assessor's comment:
The Objective of the first publication provided by the MAH in schizophrenia (Pool D[7], 1976) was to assess the efficacy of loxapine in 75 adolescents (13-18 years) with schizophrenia. Haloperidol was the active comparator of the study. This was a well-design study (double-blind, randomised, placebo-controlled). The study duration (4 weeks) could be acceptable for an acute treatment. Efficacy endpoints (BPRS, NOSIES and CGI) are validated scales. Haloperidol mean dose (9.8 mg/d for adolescent mean age 15.7 year) is equivalent to the recommended dose in adults with schizophrenia of the CCDS (1-3 mg orally TID, may be increased to 10-20 mg TID, depending on the response). Loxapine mean dose (87.5 mg/d) was into the dose interval accepted in the Physicians' Desk Reference (20-400 mg/d).

The efficacy results at weeks 4 showed no significant difference between all three treatment groups (loxapine, haloperidol and placebo) on the BPRS. The NOSIE failed to show overall significant improvement and the CGI scale showed no significant difference among the treatment groups.

Report presented by Spencer[8] (1992) was preliminary findings in an ongoing, double-blind, randomised, cross-over placebo-controlled study in 12 very young children (5.5 to 11.75 years) with schizophrenia according to the DSM-III-R criteria.
Results showed superiority of haloperidol over placebo, however these results were only preliminary findings in 12 children.

These 2 placebo-controlled short-term studies do not provide demonstration of haloperidol efficacy in the treatment of schizophrenia in adolescent between 13 and 18 years old and in children with childhood schizophrenia.

Double-blind, active-comparator-controlled studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Kumra S.[9] 1996	Superiority of CZP vs HAL for treatment-refractory children and adolescents with early-onset schizophrenia	DB, RD, vs CZP	6-week	21 CZP:10/ 7 (5M/5F) HAL:11/ 10 (6M/4F)	14.0±2.3 years	CZP: 3.07±2.59 mg/kg/d (0.34-7.53 mg/kg/d) HAL: 0.29±0.19 mg/kg/d (0.08-0.69 mg/kg/d)	6-18 years Schizophrenia as DSM-III-R criteria, with documented psychotic symptoms by 12 years, intolerance, nonresponse, or both to at least 2 different neuroleptic drugs	BPRS BHRS SANS SAPS CGAS SANRS CGI
Sikich L.[10] 2004	Effect size of RIS and OZP vs HAL in pediatric population with prominent positive psychotic symptoms	DB, RD, vs RIS and OZP	8-week	50 RIS:19 OZP:16 HAL:15	14.8±2.8 (8-19) years	RIS:4.0±1.2 mg OZP:12.3±3.5 mg HAL:5.0±2.0 mg	At least one positive psychotic symptom of moderate or greater severity on the BPRS-C the past 2 weeks	BPRS-C CGI-I CGI-S CPRS
Engelhardt DM.[11]	Comparaison of FPZ and HAL	DB, RD vs FPZ	12 weeks	30 (26M/4F)	10.2 (6-12) years	FPZ: 10.4 mg/d HAL: 10.4 mg/d	Childhood schizophrenia	CGI TESS CPRS

DB: double-blind; RD: randomised; HAL: haloperidol; CZP: clozapine, RIS: risperidone; OZP: olanzapine; FPZ: fluphenazine
BPRS: Brief Psychiatric Rating Scale; BPRS-C: BPRS-Children; BHRS: Bunney-Hambourg Rating Scale; CGI: Clinical Global Improvement, CGI-I: CGI-Improvement; CGI-S: CGI-Severity; SANS: scale for the assessment of negative symptoms, SAPS: scale for the assessment of positive symptoms, CGAS: Children's global assessment scale, SANRS: simpson-angus neurological rating scale; CPRS: Children's Psychiatric Rating Scale; TESS: treatment emergent symptoms scale.

Kumra[9] (1996) used haloperidol as active comparator to assess the efficacy of clozapine in 21 treatment-refractory children and adolescents (mean age 14.0±2.3 years) with early-onset schizophrenia, in a randomised, 6-week, double-blind, parallel-treatment study. The mean dose at the last treatment week for haloperidol was 16±8 mg/d (7-27 mg/d), or 0.29±0.19 mg/kg/d (0.08-0.69 mg/kg/d) and clozapine, 176±149 mg/d (25-525 mg/d) or 3.07±2.59 mg/kg/d (0.34-7.53 mg/kg/d).

Table 2. Clinical Ratings for Children and Adolescents With Childhood-Onset Schizophrenia at Baseline and During Clozapine and Haloperidol Treatment*

Measure	Baseline		Week 6		ANCOVA		
	Clozapine (n=10)	Haloperidol (n=11)	Clozapine (n=10)	Haloperidol (n=11)	F	*df*	*P*
Brief Psychiatric Rating Scale	83.7 (14.0)	84.7 (17.6)	52.5 (12.6)	64.7 (18.1)	5.1	2,20	.04†
Bunney-Hamburg Rating Scale	19.4 (2.8)	20.1 (6.0)	11.7 (3.3)	15.3 (3.8)	6.1	2,20	.02†
Scale for the Assessment of Negative Symptoms	77.9 (36.0)	83.0 (26.1)	46.0 (30.3)	72.2 (24.7)	13.4	2,16	.002†
Scale for the Assessment of Positive Symptoms	53.9 (25.8)	59.0 (24.9)	19.1 (11.7)	35.9 (15.6)	10.0	2,16	.01†
Children's Global Assessment Scale	26.3 (11.9)	23.2 (12.5)	44.9 (9.5)	27.9 (12.1)	9.2	2,16	.01‡
Abnormal Involuntary Movement Scale	14.7 (15.5)	14.0 (5.8)	12.1 (4.8)	12.2 (3.5)	0.01	2,15	.91
Simpson-Angus Neurological Rating Scale	12.1 (1.7)	11.9 (2.1)	12.0 (1.6)	13.9 (3.5)	1.6	2,15	.23

*Except where indicated, values are given as mean (±SD). No significant differences were found between the 2 medication groups, except for the Bunney-Hamburg Rating Scale, for which the variance for the haloperidol group is greater than the clozapine group. ANCOVA indicates analysis of covariance.
†Week 6 clozapine <week 6 haloperidol.
‡Week 6 clozapine >week 6 haloperidol.

Clozapine was statistically superior to haloperidol on all measures of psychosis (Brief Psychiatric Rating Scale, Bunney-Hambourg Rating Scale, scale for the assessment of negative symptoms, scale for the assessment of positive symptoms). Haloperidol was statistically superior to clozapine on Children's Global Assessment Scale.
The adverse effect profiles of the 2 medications were similar except that drowsiness and salivation were statistically greater with clozapine, while haloperidol produced statistically more insomnia. The relatively high mean haloperidol dose did not result in an increase in extrapyramidal adverse effects, but this could have been masked by the prophylactic benztropine. Five patients who received clozapine experienced neutropenia, resulting in discontinuation for 2 of the subjects. Two patients in the double-blind clozapine trial had clinically significant seizure activity, resulting in discontinuation of clozapine. One subject was dropped from the study in the fifth week of haloperidol treatment because of early signs of neuroleptic malignant syndrome which normalized within a few days after discontinuation of haloperidol.

Sikich[10] (2004) conducted a randomised, 8 week, double-blind, parallel-treatment study to estimate the acute antipsychotic effect size and side effect propensity of risperidone (n=19) and olanzapine (n=16) in a paediatric population aged 8 to 19 years (mean [SD] age,14.8 ± 2.8), in comparison to haloperidol (n=15).
Patients were selected on the basis of having at least one positive psychotic symptom of moderate or greater severity on the Brief Psychiatric Rating Scale for Children (BPRS-C), which had been present throughout the past 2 weeks, and full scale IQ greater than 69. Permitted primary diagnoses were Psychosis NOS, Schizophreniform Disorder, Schizophrenia, Schizoaffective Disorder, Delusional Disorder, Major Depression with Psychotic Features, and Bipolar Affective Disorder with Psychotic Features.
The computer-generated randomisation schedule was stratified by age (8–11 years or ≥12 years) in order to ensure that younger children, who might have different metabolism or adverse reactions to the medications, were equally represented in all treatment groups.
The dose of medication was titrated to a moderate target dose (risperidone: 0.5–3 mg in 0.5 mg increments, olanzapine: 2.5–12.5 mg in 2.5 mg increments, and haloperidol: 1–5 mg in 1mg increments) over 1–2 weeks, determined by participant response and side effects. The mean (±SD) antipsychotic doses used at termination were risperidone 4.0±1.2 mg, olanzapine 12.3±3.5 mg, and haloperidol 5.0±2.0 mg.
The primary outcome measure for the within group analyses was the change in the BPRS-C total score from baseline to end point.

At the end of acute treatment, the response status of each subject (defined by a Clinical Global Impressions-Improvement (CGI-I) score of '1' or '2' and at least a 20% reduction in the BPRS-C total score) was determined. Those who responded were eligible to continue double-blind treatment for an additional 12 weeks.

50 children and adolescents between the ages of 8 and 19 years were enrolled in the study: 19 participants were randomised to risperidone treatment, 16 to olanzapine treatment, and 15 to haloperidol treatment. The demographic and psychiatric characteristics of the sample were homogeneous across treatment groups. The mean age was 14 years 8 months (SD=32 months, range 8 years 4 months–19 years 8 months). Of these, 60% were male, 60% were Caucasian, 32% were African-American, and 4% each were Native American and Hispanic.

Participants were severely ill with a mean (±SD) CGI severity score of 5.6 (±1.1) and a mean (±SD) BPRS-C total score of 51.3 (±12.4). Most (74%) were hospitalised at enrolment. Most (78%) were experiencing their first episode of psychosis.

Marked reductions in the total BPRS-C scores were observed in each of the treatment groups (Tables 3a and b). Between baseline and endpoint, a reduction of BPRS-C score of 50 % was observed in risperidone group (SR=-84.5, p=0.0018), of 66% in the olanzapine group (SR=-66.0, p=0.0018), and of 33% in the haloperidol group (SR=-45.0, p=0.014). Similar, statistically significant reductions were observed in the positive symptoms subscale score of the CPRS, in all treatment groups. The negative symptoms subscale score of the CPRS was significantly reduced in the risperidone group, but not in the olanzapine or haloperidol groups.

However, in the haloperidol-treated group, reductions in the total CPRS, CGI-S, or CGI-I scores were not statistically significant. Over the course of the entire trial, 36/50 (72%) of participants met criteria for positive responder status. Response rates of 74% (14/19) with risperidone, 88% (14/16) with olanzapine, and 53% (8/15) with haloperidol were observed. Between-group comparisons of the magnitude of improvement within the psychopathology outcomes failed to detect statistical differences (Tables 3a and b).

However, there were differences in the mean time to response: 1.6 (±1.3) weeks in individuals treated with olanzapine, 2.3 (±1.8) weeks in those treated with risperidone, and 2.4 (±1.3) weeks in those treated with haloperidol (log-rank test: χ^2=6.21, df=2, p<0.045).

Table 3a Acute Symptom Reduction Associated with Treatment

	Risperidone (*N* = 19)					Olanzapine (*N* = 16)					Haloperidol (*N* = 15)					Group differences	
Rating[a]	Baseline	Week 8 or end point	SR	Corrected *p*[b]	Effect size	Baseline	Week 8 or end point	SR	Corrected *p*	Effect size	Baseline	Week 8 or end point	SR	Corrected *p*	Effect size	K–W χ^2	*p*
BPRS-C	54 ± 13	27 ± 20	−84.5	0.0018	−1.44	50 ± 10	22 ± 12	−66.0	0.0018	−1.69	49 ± 14	33 ± 19	−45.0	0.012	−0.79	3.22	0.200
CPRS-total	114 ± 32	60 ± 48	−79.0	0.0018	−1.13	105 ± 25	53 ± 27	−51.5	0.0036	−1.69	110 ± 35	70 ± 39	−36.5	0.285	−0.79	1.75	0.416
CPRS-positive	27 ± 7	14 ± 12	−78.5	0.0018	−1.12	30 ± 7	11 ± 9	−58.5	0.0036	−1.82	31 ± 6	17 ± 11	−48.0	0.015	−1.22	2.76	0.252
CPRS-negative	22 ± 15	10 ± 8	−70.5	0.005	−1.00	17 ± 14	11 ± 9	−17.0	0.60	−0.52	18 ± 9	11 ± 10	−20.5	0.96	−0.72	0.76	0.47
CGI-severity	5.8 ± 1.2	3.8 ± 1.3	−57.5	0.0054	−1.22	5.3 ± 1.2	3.6 ± 1.3	−45.5	0.0036	−1.45	5.6 ± 1.0	4.5 ± 1.2	−19.0	0.705	−0.66	5.50	0.064
CGI-improvement	4 ± 0	2.1 ± 1.2	−86.0	0.0018	−1.58	4 ± 0	2.0 ± 1.1	−59.0	0.0018	−1.83	4 ± 0	2.7 ± 1.3	−37.5	0.075	−1.03	3.82	0.15

Table 3b Overall Response Associated with Treatments

Rating[a]	Risperidone (*N* = 19)	Olanzapine (*N* = 16)	Haloperidol (*N* = 15)	Group differences Fisher's exact
Responders at week 8[c], *n* (%)	14 (74)	14 (88)	8 (53)	0.12
CGI-I of '1', *n* (%)	6 (32)	5 (31)	2 (13)	0.44

[a]All values are LOCF to week 8. All numeric values are shown as the mean ± SD.
[b]The *p*-values within each treatment group have been corrected for multiple comparisons within the group by multiplying by 6.
[c]Responders were defined *a priori* as having a CGI of '1' or '2' and a 20% or greater reduction in the BPRS-C total score.

SR= signed rank

Table 5 Reasons for Withdrawal

	N (%) (week of withdrawal)[a]			Group differences
	Risperidone (N = 19)	Olanzapine (N = 16)	Haloperidol (N = 15)	Fisher's exact p-value
Insufficient response	2 (11) (3,7[b])	2 (13) (1,5)	1 (7) (6[b])	1.000
Side effects[c]	5 (26) (1,3,4,6,7[b])	0 (0)	7 (47) (2,2,2,3,3,3,6[b])	0.005
EPS	1 (5) (1)	0 (0)	5 (33) (2,2,3,3,6[b])	0.009
Weight gain	3 (16) (4,6,7[b])	0 (0)	0 (0)	0.101
Other	1 (5) (3)	0 (0)	3 (20) (2,3,3)	0.136
Noncompliance	2 (11) (4,6)	0 (0)	0 (0)	0.323
Moved to remote site[d]	1 (5) (4)	0 (0)	0 (0)	1.000
Total withdrawals	9 (47) (1,3,3,4,4,4,6,6,7)	2 (13) (1,5)	7 (47) (2,2,2,3,3,3,6)	0.058

[a]The week that each subject withdrew for that reason is shown in brackets in order to provide a sense of the time course of such events.
[b]Subject withdrew as a result of both insufficient response and intolerable side effects (weight gain for the risperidone-treated subject and extrapyramidal symptoms for the haloperidol-treated subject).
[c]The withdrawals due to any side effect are shown first, with those due to specific side effects listed below. In the haloperidol, group one subject withdrew as a result of both EPS and anticholinergic side effects.
[d]If the subject who moved to a remote site is excluded from this analysis, 8/18 (44%) in the risperidone group withdrew.

Side effects were frequently observed in this paediatric sample. More than half of the subjects treated with either atypical medication had evidence of mild to moderate Parkinsonian symptoms and two of the 19 subjects treated with risperidone had severe EPS (data not shown). Further, a large proportion of those in each treatment group required low-dose anticholinergics to control their EPS (haloperidol-67%, olanzapine-56%, risperidone-53%).
In most subjects (23 of 30), anticholinergics were continued throughout the remainder of the trial. The final benztropine dose was not different between treatment groups.
Two individuals with acute and severe dystonic reactions in the haloperidol group were withdrawn from the study prior to starting anticholinergics. Between-group comparisons of maximal EPS demonstrated more frequent and severe symptoms in the haloperidol group.
Four subjects reported akathisia at end point; two were treated with haloperidol and two with olanzapine. Significant weight gain was observed in all treatment groups (risperidone: 4.9 (±3.6) kg; olanzapine: 7.1 (±4.1) kg; haloperidol 3.5 (±3.7) kg).
There were three safety parameters, which changed significantly between baseline and end point. In the haloperidol-treated group, there was a small increase in the QTc from 394 (±18) to 402 (±16) ms, SR 18.5, p=0.031. Similar increases were not observed in the atypical antipsychotic-treated groups. In the risperidone-treated group, increases were observed in two liver function tests: aspartate aminotransferase (AST) increased from 21.9 (±5.4) U/l to 28.1 (±10.8) U/l, SR 35, p=0.046 and alanine aminotransferase (ALT) increased from 20.9 (±11.9) U/l to 32.9 (±23.8) U/l, SR 39.5, p=0.0104. There was also a trend toward an increase in the random glucose within the olanzapine-treated group from 87.2 (±10.8) mg/dl to 97.2 (±14.4) mg/dl, SR 18.5, p=0.0645. However, the clinical significance of these increases is unclear.
Although the mean end point prolactin level was greater in the risperidone-treated group (37.2±19.8 ng/ml) than the other groups, (olanzapine 30.0±12.9 ng/ml and haloperidol 32.2±29.0) this difference was not significant.

Engelhardt DM.[11] (1973) evaluated fluphenazine (N=15; mean weight 34.5 kg) and haloperidol (N=15; mean weight 36.2 kg) in an outpatient group of 30 schizophrenic children (6-12 years) with a primary diagnosis of childhood schizophrenia. The starting dose was 2 to 4 mg per day. The daily dose was then increased by the child psychiatrist, depending on individual response, until a maximum daily dose of 16 mg.
The most consistent problems present in all children were disturbances of speech and communication, motor activity, affect, attention and concentration, relatedness to peers and to people in general. All children were hyperkinetic and exhibited motor stereotypies. All functioned

at moderately to severely retarded levels. At the start of the study 19 children were considered extremely or severely ill, eight markedly ill, and three rated as moderately ill on a 7-point scale.

Table 3

Psychiatrist's Global Ratings of Change (CGI)

Global rating of change	Fluphenazine		Haloperidol	
	N	Percent	*N*	Percent
Very much improved	5	33	7	47
Much improved	9	60	6	40
Minimally improved	1	7	2	13
Very much worse	0	0	0	0
Total	15	100	15	100

All children were considered to have demonstrated some degree of global improvement following treatment with either drug. Ninety-three percent of the children treated with fluphenazine and 87% of those treated with haloperidol were rated as much or very much improved.

An analysis of the morbidity scores of the CPRS-1 indicated statistically significant decrease in severity for the fluphenazine group from a baseline mean of 54.0 to a post-treatment mean of 42.4. For haloperidol, there was a statistically significant decrease from a baseline mean of 48.7 to a post-treatment mean of 37.6 with no statistical difference between the two drug groups in response to treatment.

A comparison of baseline with Week 12 scores indicated significant improvement for both drug groups on 9 of the 19 items of the CPRS-1. These items were psychomotor activity, stereotyped motor behaviour, responsiveness, relations with adults and with children, frustration tolerance, concentration, eating habits, and sleeping. Fluphenazine treatment produced significant improvement as well in self-awareness, constructive play, compulsive acts, and self-mutilation. Haloperidol treatment yielded significant improvement in coordination, self-care, affect, and exploratory behaviour. However, no significant differences between drug groups on any of the 19 items were observed.

Unlike the significant improvement observed in both drug groups on many of the first 19 items, only one item dealing with language and communication was affected by drug treatment. Haloperidol treatment resulted in significant improvement in "range of communication," i.e., the amount of information a child was able to communicate disregarding the level of his verbal productions and the mode of communication. However, no significant difference between the two drugs on this item was observed.

Side effects were relatively infrequent and tended to be mild. Of the 15 children on fluphenazine and 7 of the 15 children on haloperidol were free of side effects for the entire 12-week treatment period. The side effects most frequently noted were extrapyramidal symptoms (EPS), with increased salivation being the most commonly encountered symptom. EPS were observed more frequently on fluphenazine than on haloperidol.

Of the remaining side effects, drowsiness was the most common; it was controlled by dose reduction. In most children weight gain was observed over the course of treatment. On fluphenazine (N = 14), the average weight gain was 0.95 kg, with 11 children gaining weight and 3 suffering a weight loss. The tendency toward weight gain was greater on haloperidol, with the average group weight gain being 1.7 kg. Fourteen of the 15 children gained weight and only one child suffered a weight loss.

Assessor's comment:

The MAH provided 3 double-blind, active-comparator-controlled studies in acute exacerbation of symptoms of schizophrenia. With the lack of placebo-arm, no internal-validation of these studies is possible. The use of placebo-arm in short term study is considered necessary even in children

and adolescents, as it has been confirmed in recent studies with atypical antipsychotics (aripiprazole).

Kumra[9] (1996) used haloperidol as active comparator to assess the efficacy of clozapine in 21 treatment-refractory children and adolescents. Clozapine was superior to haloperidol in all outcomes measures (BPRS, BHRA, SANS, SAPS).

The publication of Sikich[10] (2004) is the most complete. The authors used haloperidol as active-comparator to estimate the acute antipsychotic effect size and side effect propensity of risperidone and olanzapine. 50 children and adolescents aged 8 to 19 years (14.8±2.8 years) were randomised between risperidone (19), olanzapine (16) and haloperidol (15) in a double-blind 8-week study. Most (78%) were experiencing their first psychotic episode. Statistically significant reductions in total BPRS-C score were observed in each of the treatment groups between baseline and endpoint (reduction of 50% in risperidone group, 66% in olanzapine group and 33% in haloperidol group). Response rates (defined by a CGI-I score of 1 or 2 and at least a 20% reduction in the BPRS-C total score) of 74% with risperidone, 88% with olanzapine and 53% with haloperidol were observed. There was no significant difference between treatment groups. This study tended to show efficacy of haloperidol in children and adolescents with schizophrenia or first psychotic episode. However, its draw-backs are the lack of placebo-arm to confirm assay sensitivity and the small number of patients in each treatment groups.

Engelhardt[11] (1973) evaluated the efficacy of 12-week treatment with fluphenazine or haloperidol in 30 very young children (6-12 years) with childhood schizophrenia. Analyses showed significant decrease in severity for both drugs from baseline to post-treatment and no difference between treatment groups on CPRS.

Open-label, active-comparator-controlled studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatment	Diagnosis Incl. criteria	Outcomes/ endpoints
Gothelf D.[12] (2003)	Comparison of OZP, RIS and HAL	OL	8-week	43 pts OZP:19 RIS:17 HAL:7	OZP: 16.8±1.6 y RIS: 17.0±2.1 y HAL: 17.1±1.3 y	OZP: 12.9±3.1 mg/d RIS: 3.3±1.1 mg/d HAL: 8.3±3.8 mg/d	Schizophrenia as DSM-IV	PANSS UKU
Green WH.[13] (1992	Comparison of, CPZ, TDZ, TFZ and HAL	OL Retro-spective	-	38 pts CPZ: 12 TDZ: 7 TFZ: 7 HAL: 15	5.7-11.11 y	CPZ: 75-100 mg/d TDZ: 175-450 mg/d TFZ: 2-13 mg/d HAL: 1-6 mg/d	Schizophrenia as DSM-III	WISC CBI

OL: open-label; HAL: haloperidol; OZP: olanzapine; RIS: risperidone, CPZ: chlorpromazine, TDZ: thioridazine, TFZ: trifluoperazine
PANSS: Positive and negative syndrome scale; UKU: Udvalg for Kliniske Undersogelser Side Effect Rating Scale
WISC: Wechsler Intelligence Scale for Children, CBI: children's behaviour inventory

Gothelf D.[12] (2003) evaluated and compared the drug response and side effects in 43 adolescents with schizophrenia treated with olanzapine (n=19), risperidone (n=17), and haloperidol (n =7) in an 8-week open trial. Seven patients were drug-naïve, and 36 had been previously treated with antipsychotic agents either classical or atypical. All three drugs were started at a low dose, with stepwise increments. The allocation of the patients to the three study groups and the dosages required were based on the clinical judgment of the departmental directors.

The severity of the psychiatric symptomatology was measured with the PANSS), and the neuroleptic side effects with the comprehensive Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale. The UKU is composed of 48 adverse effects items, divided into 4 categories: psychic, neurologic, autonomic, and other. Each item is rated on a 4-point scale: 0– no side effects, 1– mild, 2– moderate, 3– severe. According to the author, this scale has been found to be reliable and valid and has been used in many studies of antipsychotic drugs.

Starting doses were 0.5 mg per day for risperidone and haloperidol, and then increased by 0.5 mg every one to 2 days, and 5 mg per day for olanzapine, and then increased by 2.5 mg every one to 2 days. The final mean doses (±SD) for risperidone were 3.3±1.1 mg per day (range 1–5), for olanzapine 12.9±3.1 mg per day (range 10–20), and for haloperidol 8.3±3.8 mg per day (range 5–15). The final mean doses stated in mg/kg were 0.05±0.02 mg/kg for risperidone, 0.2±0.1 mg/kg for olanzapine and 0.1±0.1 mg/kg for haloperidol.

Of the 43 patients who started the study, 39 completed the full 8 weeks of treatment. Four patients dropped out before the end of the study period. Two (1 from the risperidone and 1 from the olanzapine group) had a psychotic exacerbation and 2 (1 risperidone and 1 olanzapine) refused to continue hospitalization and were noncompliant with treatment. None of the patients discontinued a medication because of side effects.

Results showed that significant clinical improvement was observed by week 4 for all medications. Olanzapine and haloperidol induced fatigability more frequently than risperidone. Haloperidol was associated with a higher frequency of depression and more severe extrapyramidal symptoms. The authors concluded that olanzapine, risperidone and haloperidol appeared to be equally effective for the treatment of schizophrenia in adolescent inpatients but had different side effect profiles.

Table 3. Effects of risperidone, olanzapine and haloperidol on PANSS scores (mean ± SD)

	Baseline	Week 4	Week 8
	Positive symptoms		
Risperidone (n = 15)	17.4 ± 6.9	12.8 ± 3.4	13.2 ± 3.8
Olanzapine (n = 17)	15.0 ± 4.9	11.7 ± 4.2	13.3 ± 8.0
Haloperidol (n = 7)	21.3 ± 8.9	14.1 ± 6.3	13.0 ± 5.8
Effects of Week		$F(2,72) = 16.9, p < 0.001$	
Drug X week interactions		$P = 0.14$	
	Negative symptoms		
Risperidone (n = 15)	24.2 ± 9.3	20.3 ± 8.8	20.8 ± 8.4
Olanzapine (n = 17)	18.1 ± 11.0	13.8 ± 6.4	14.9 ± 8.0
Haloperidol (n = 7)	20.3 ± 8.0	16.0 ± 9.1	16.4 ± 8.5
Effects of week		$F(2,72) = 5.3, p < 0.01$	
Drug X week interactions		$P = 0.99$	
	Total Scores		
Risperidone (n = 15)	90.2 ± 26.4	73.3 ± 9.2	73.9 ± 19.1
Olanzapine (n = 17)	71.6 ± 23.8	57.7 ± 14.8	61.6 ± 28.4
Haloperidol (n = 7)	86.1 ± 24.4	66.4 ± 19.6	66.3 ± 21.8
Effect of Week		$F(2,72) = 12.7, p < 0.001$	
Drug X week interactions		$P = 0.99$	

PANSS positive and negative syndrome scale

Table 5. Rate of extrapyramidal side effects in adolescent patients treated with risperidone, olanzapine and haloperidol

	Risperidone (n = 17)	Olanzapine (n = 19)	Haloperidol (n = 7)	Chi-square
Any EPS	4 (23.6%)	3 (11.8%)	4 (57.2%)	4.66, p = 0.01
Dystonia	1 (5.9%)	0	2 (28.6%)	6.48, p = 0.04
Rigidity	0	1 (5.3%)	3 (42.9%)	11.45, p = 0.003
Hypokinesia/akinesia	2 (11.8%)	1 (5.3%)	2 (28.6%)	2.70, p = 0.26
Tremor	2 (11.8%)	2 (10.5%)	1 (14.3%)	0.07, p = 0.96
Akathisia	1 (5.9%)	0	3 (42.9%)	11.52, p = 0.003

Green et al.[13] (1992) compared on an open basis haloperidol to chlorpromazine, thioridazine and trifluoperazine in 35 hospitalized children with ages between 5.7-11.11 years and diagnosed with schizophrenia. All received trials of one or more neuroleptics. Twelve children received chlorpromazine, 7 received thioridazine, 15 received haloperidol, and 7 received trifluoperazine. For haloperidol they reported that the optimal dose ranged between 1 and 6 mg/day. Overall, these 35 children were relatively treatment resistant and clinical response to medication was disappointing. At optimal doses, none of the four drugs appeared clinically to be notably superior to the others in controlling symptoms. For haloperidol only eight (53.35%) subjects improved sufficiently that they were maintained on the drug; the seven other children (46.78%) failed to respond adequately or developed side effects, usually acute dystonic reactions which necessitated a change in drug. Acute dystonic reactions occurred in approximately 25% of the children treated with haloperidol despite low initial doses and gradual increments of the drug. The most common side effect for all drugs was sedation.

Assessor's conclusion on use of haloperidol in children with schizophrenia:

Schizophrenia is not typically a disorder of children; the disease is very rare in pre-pubertal children. In this respect it would be more realistic to speak about first episode of psychosis in children which in some cases might finally crystallize as early onset schizophrenia.
The MAH provided 7 publications: 2 publications were double-blind, placebo-controlled studies, 3 were double-blind, active-comparator-controlled, and 2 were open-label with active-comparator.

No well-designed studies (double-blind, placebo-controlled, randomised, parallel, 6-week, with PANSS or BPRS as primary endpoint) were performed with haloperidol in children and/or adolescent with schizophrenia. Placebo-arm in short-term study is considered necessary to assess efficacy of treatment in schizophrenia in children and adolescents. No long-term efficacy/safety studies were available.

Across studies, haloperidol treatment was associated with the following adverse effects: Extrapyramidal symptoms (acute dystonic reaction, akathisia, and increased salivation), sedation/drowsiness, weight gain, one case of neuroleptic malignant syndrom, QTc prolongation.
The most frequent adverse events were EPS and sedation/drowsiness.
Frequency of Extrapyramidal symptoms may be underestimated because of anticholinergic treatment frequently associated with haloperidol treatment.

The dosages used through these studies were not always stated per weight. Mean doses ranged from 2.02 mg/d (0.02-0.12 mg/kg/d) in very young children with childhood schizophrenia (Spencer[8], 1992) to 16 mg/d (0.08-0.69 mg/kg/d) in treatment-refractory children and adolescents with schizophrenia (Kumra[9],1996). Slow titration seems to be used in every study.

These studies did not provide sufficient evidence of haloperidol efficacy in the short-term and long-term treatment of schizophrenia in adolescent between 13 and 18 years old or in children with childhood schizophrenia. Furthermore, the safety profile, mainly Extrapyramidal symptoms and especially dyskinesia, is of concern in paediatric population.
In conclusion, no recommendation based of these data of use of haloperidol in childhood schizophrenia or in adolescents with schizophrenia could be made.

5.2 Use in Tourette's Disorder (TD) and Tic disorder

The MAH provided 9 publications on use of haloperidol in paediatric population with Tourette's disorder and Tic disorder. Four publications were placebo-controlled studies, 4 were active-comparator-controlled studies, and 1 was open-label study. (See tables below)

Placebo-controlled studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Shapiro E.[14] (1989)	Comparison of efficacy and adverse effects of HAL and PZD	RD, DB, parallel and cross-over vs PZD and PLA	Parallel (HAL/PZD/ PLA) period 1 of 6 weeks followed by cross-over (HAL/PZD) period 2 of 6 weeks	57 pts Period 1: HAL:18 PZD:20 PLA:19	21.1±11.0 y (8-46 y)	HAL: 4.5±2.7 mg PZD: 10.6±7.1 mg	8-65 y with DSM-III criteria of Tourette Syndrome	TS-SS CGI Videotape ratings
Borison RL.[15] (1981)	To find therapeutic alternatives to HAL 3 studies	1: blinded pts vs CLO and PLA 2: blinded vs FPZ, TFZ and PLA 3: single-blind PLA vs LI	1: 9 weeks	1: 22 (14/8) 2: 10 (9/1) 3: 10	1: 16y (8-44 y) 2: 20.5y (12-43y) 3: 10-42 y	1: CLO: 0.25-0.9mg/d HAL: 2.5-8.5 mg/d 2: HAL: 5-20mg/d FPZ: 8-24mg/d TFZ: 10-25mg/d 3: LI: 0.6-1.5 mEq/l		
Connell[16] (1967)	Drug treatment of adolescent tiqueurs	1: RD, DB, cross-over DZP vs PLA 2: : RD, DB, cross-over HAL vs PLA	1: 2 w	4 pts	14.25y (12-16y)	1: DZP: 2 mg tid 2: HAL : 1-5 mg bid	Adolescent tiqueurs	Number of Tics Anxiety level Behaviour rating scale Effect of different experimental conditions on the measurement of tic frequency
Sallee[17] (1997)	Efficacy and safety of PZD and HAL	DB, RD, 24-week, vs PLA and PZD double cross-over	3 x 6 w	22 pts (17/5)	10.2 ± 2.5 y (7-16y)	HAL: 3.5 ± 2.2 mg/d PZD: 3.4 ± 1.6 mg/d	Tourette's disorder as DSM-III-R	TSGS CGI

DB: double-blind; RD: randomised, PLA: placebo; HAL: haloperidol; PZD: pimozide; CLO: clonidine, FPZ: fluphenazine, TFZ: trifluoperazine, LI: lithium, DZP: diazepam, pts: patients
TS-SS: Tourette syndrome severity scale, CGI: Clinical Global Impression, TSGS: Tourette syndrome global scale

The study of Shapiro[14] (1989) compared the effectiveness of haloperidol, pimozide, and placebo using a double-blind parallel and crossover design in children, adolescents and adults (number of patients by age range is not specified). The parallel study included an initial single-blind three-week baseline period of placebo treatment, followed by random assignment to treatment with haloperidol, pimozide, or placebo for six weeks (period 1). At the end of period 1, patients entered the crossover segment (period 2). Patients randomly assigned initially to six weeks of treatment with either haloperidol or pimozide were crossed over to six weeks of treatment with the alternate medication. Patients assigned initially to six weeks of treatment with placebo were then randomly and blindly assigned to treatment with haloperidol or pimozide for six weeks and then crossed over to treatment with the alternate drug for six weeks.
None of the patients developed withdrawal effects.
57 patients completed the parallel phase of the study (pimozide=20, haloperidol=18, placebo=19) The mean age of the patients was 21.1±11.0 years (range, 8 to 46 years). The mean daily dose at end point was 4.5±2.7 mg for haloperidol and 10.6+7.1 mg for pimozide. The mean dosage at end point was 0.08±0.05 mg/kg/d (*0.0* to 0.17 mg/kg/d) for haloperidol and 0.18±0.12 mg/kg/d (0.02 to 0.51 mg/kg/d) for pimozide.

Table 2.—Unadjusted Means for Dependent Variables at End Point for Placebo (n = 19), Haloperidol (n = 18), and Pimozide (n = 20) in Parallel Study

	Mean ± SD		
	Placebo	Haloperidol	Pimozide
TS Severity Scale, physician*	2.9 ± 2.5	1.2 ± 1.2	2.5 ± 3.0
Videotape counts, No./min			
Total motor tics	9.5 ± 5.8	6.8 ± 8.0	5.7 ± 7.9
Total vocal tics	0.7 ± 1.2	0.2 ± 0.3	0.5 ± 1.1
Clinical Global Impression Scale			
Therapeutic effect			
Patient	1.9 ± 2.1	3.5 ± 1.4	3.2 ± 1.6
Physician	1.9 ± 2.1	3.4 ± 1.5	3.2 ± 1.5
Adverse effects			
Patient	0.9 ± 1.2	1.9 ± 1.4	1.3 ± 1.3
Physician	0.8 ± 1.2	1.8 ± 1.3	1.3 ± 1.0
% decrease of tics, patient	43.4 ± 34.5	65.0 ± 26.5	60.1 ± 31.3

*TS indicates Gilles de la Tourette's syndrome.

Table 3.—ANOVA for Outcome Variables at End Point for Placebo (n = 19), Haloperidol (n = 18), and Pimozide (n = 20) and Least Significant Difference for Haloperidol vs Placebo and Pimozide vs Placebo in Parallel Study*

	P		
	Overall ANOVA	Haloperidol vs Placebo	Pimozide vs Placebo
Clinical Global Impression Scale			
Therapeutic effect			
Patient	.021	.010	.030
Physician	.017	.009	.022
Adverse effects			
Patient	.052	.016	NS
Physician	.034	.010	NS
% decrease of tics, patient	.091	.039	.099

*ANOVA indicates analysis of variance; NS, not significant.

Table 4.—Results of Analysis of Covariance With Baseline Values as Covariates for Dependent Variables at End Point for Placebo (n = 19), Haloperidol (n = 18), and Pimozide (n = 20) in Parallel Study*

	Adjusted Means			P		
	Placebo†	Haloperidol	Pimozide	Test for Homogeneity of Regression	Haloperidol vs Placebo	Pimozide vs Placebo
TS Severity Scale, physician	3.2/2.8	1.2	2.6	.002‡	.001§	NS
Videotape counts, No./min						
Total motor tics	28.1/28.6	20.8	16.9	.029‡	NS	.058
Total vocal tics	1.9/1.9	0.7	1.7	.020‡	.019§	NS

*TS indicates Gilles de la Tourette's syndrome; NS, not significant.
†Expressed as adjusted means for placebo compared with haloperidol/placebo compared with pimozide.
‡That is, the regressions have heterogeneous slopes. Separate analyses of covariance (haloperidol vs placebo, pimozide vs placebo) were performed on these variables.
§Test for homogeneity of regression still significant.

During the period 1, treatment with haloperidol resulted in statistically significantly greater improvement than placebo on four of the six dependent efficacy variables at endpoint (Tables 3 and 4), and the unadjusted means for two non-significant variables were in the expected direction (Table 2). Treatment with pimozide resulted in significantly greater improvement than

treatment with placebo at endpoint for two of the six variables and non-significant trends for two variables, and the unadjusted means were in the expected direction for the two remaining variables (Tables 3, and 4).

Table 7.—Analyses of Variance for Period Effect and Drug Effect (Haloperidol vs Pimozide) in Crossover Design*

Variables	P	
	Period Effect	Drug Effect
TS Severity Scale, physician	.286	.011†
Videotape counts‡		
Total motor tics	.016	.427
Total vocal tics	.669	.583
Clinical Global Impression Scale		
Therapeutic effect		
Patient	.335	.609
Physician	.141	.554
Adverse effects		
Patient	. . .	.156§
Physician	.812	.812
% decrease of tics, patient	.244	.437

*TS indicates Gilles de la Tourette's syndrome.
†Haloperidol significantly better than pimozide.
‡Log transformation.
§*t* test for first period only because of carryover effect.

Table 8.—Unadjusted Means for Dependent Variables at End Point for Haloperidol and Pimozide (N = 55) in Crossover Study*

	Mean ± SD			
	Haloperidol		Pimozide	
TS Severity Scale, physician	1.4	1.5	2.0	2.3
Videotape counts, No./min				
Total motor tics	5.6	6.3	5.2	6.4
Total vocal tics	0.3	0.7	0.4	0.8
Clinical Global Impression Scale				
Therapeutic effect				
Patient	3.5	1.5	3.4	1.6
Physician	3.6	1.5	3.4	1.5
Adverse effects				
Patient	1.6	1.3	1.8	1.3
Physician	1.6	1.2	1.6	1.2
% decrease of tics, patient	67.0	28.1	64.4	30.6

*TS indicates Gilles de la Tourette's syndrome.

During the period 2, pimozide was not more effective than haloperidol on any of the eight efficacy outcome variables, and haloperidol was statistically significantly more effective than pimozide on the TS Severity Scale rated by the physician (Tables 7). On the Treatment Preference Scale, haloperidol was ranked as most efficacious by 29 patients, pimozide by 24, and placebo by one: one patient declined to rank the treatments.
One patient treated with haloperidol developed acute dystonia, 9 developed akathisia.

Borison[15] (1981) has carried-out pharmacological trials aimed at finding therapeutic alternatives to haloperidol, which may produce equivalent therapeutic efficacy with fewer side-effects. They compared in separate studies haloperidol in the indication Tourette's disorder to clonidine, fluphenazine, trifluoperazine and lithium in children, adolescents and adults (number of patients by age range is not specified).
Comparison with Clonidine: 22 patients ranging in age from 8-44 years (mean=16 years) who had been symptomatic with Tourette's disorder for an average of 8.5 years were included a study. The minimum duration of treatment with each medication was nine weeks. A flexible dosage design was used, allowing for increasing the dosage of medication until either full suppression of the tics occurred or side-effects intervened.
Assessment of efficacy was made using a global assessment scale for tics.
When comparing baseline tic scores without treatment to treatment tic scores, the authors found that both haloperidol and clonidine produce significant therapeutic benefit, whereas placebo did not. However, there was no statistical difference when comparing clonidine to haloperidol.
The onset of therapeutic benefit with haloperidol was usually abrupt, often first becoming noticeable at daily doses of 1.5 mg or greater. This was not true with clonidine which appeared to have a slower onset of the therapeutic action over a period of weeks which generally did not become apparent until doses of approximately 0.45 mg daily were obtained.
The major side-effects encountered with haloperidol administration were sedation (15/22), lethargy (12/22), depression (5/22), akathisia (9/22), pseudoparkinsonism (6/22) and dystonic reactions (3/22). The major side-effects associated with clonidine use included dry mouth (5/22), sedation (4/22), dizziness and palpitations (2/22), and insomnia (1/22). In placebo group, the major side-effects were dry mouth (2/22) and insomnia (2/22).

Comparison of Fluphenazine and Trifluoperazine with haloperidol: ten patients participated in the study with a mean age of 20.5 years (range of 12-43 years) who had been ill with GTS for an average of 10.2 years. The study was run using a blind placebo controlled design with haloperidol being compared to fluphenazine and trifluoperazine. A flexible dosage regimen was used with patients incrementally increasing their dose until either full tic suppression occurred or the maximum dose with tolerable side-effects was achieved. The range of dosages was 5-20 mg for haloperidol, 8-24 mg for fluphenazine and 10-25 mg for trifluoperazine.
When compared to placebo, all three drugs produced statistically significant therapeutic actions in tic suppression. None of the three agents statistically proved to be more efficacious than the other.
They found that the most dramatic differences among the three drugs occurred in the side-effect profile. Haloperidol produced a statistically significant higher incidence of sedation and extrapyramidal side-effects than did the other two neuroleptics.
In six patients, using an open design the authors combined haloperidol with either trifluoperazine or fluphenazine after achieving maximal therapeutic effects with haloperidol. The drugs were additive only in their side-effects and not in their therapeutic actions.

Comparison with Lithium: ten subjects participated in the study and ranged in age from 10 to 42 years and had been symptomatic with Tourette's disorder from 3 to 32 years. In three of the ten cases, patients were maintained on stable dosages of haloperidol and benztropine while receiving Lithium treatment. The serum levels of Lithium achieved ranged between 0.6 and 1.5 mEq/l. Results showed that the use of lithium was without significant action upon lessening the tics of Tourette's disorder.
The authors concluded that fluphenazine and trifluoperazine were found to be as efficacious as haloperidol but with fewer side-effects; clonidine was shown to be equally efficacious. Lithium had no significant effect on the symptoms of Tourette's disorder.

Connell[16] (1967) conducted a double-blind placebo controlled trial to compare the use of haloperidol and diazepam in 4 adolescents with tics.
Diazepam trial: the trial was carried out over a period of two weeks divided into four periods of three and a half days. Each patient received diazepam for two of the periods in a dosage of 2 mg t.i.d., and placebo for the other two. An analysis of variance was performed to examine for differences in tic frequency while receiving diazepam and placebo, but none of the comparisons approached an acceptable level of significance.
Haloperidol trial: the trial of haloperidol utilized essentially the same design as that used with diazepam, with the modification that each drug and placebo period was extended to two weeks, in order to allow for the longer excretion time of haloperidol. Haloperidol was given in a dose of 1-5 mg b.i.d. Two subjects developed mild dystonic side-effects and two subjects also developed mild akathisia.
The authors observed that Haloperidol reduced tic frequency in all 4 cases, although more in some than in others, and although significant differences did occur between subjects, the drug effect was more marked, and is demonstrated despite these individual differences. Subject I, who appeared to respond best to diazepam, also showed the most marked response to haloperidol. As hypothesised, the tic frequency is also significantly related to the conditions of measurement.
The authors concluded that diazepam was found to have no significant effect on the frequency of the tics when a dosage of 2 mg. t.i.d. was used and that haloperidol was highly efficient in reducing the frequency of tics. It was also demonstrated that the conditions of measurement affect the tic frequency, which was greater whilst reading aloud. Haloperidol appeared particularly effective in preventing increase of the tics under such conditions of stress.

Salle[17] (1997) evaluated the relative efficacy and safety of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome in 22 children and adolescents aged 7-16 years. A double-blind, 24-week, placebo-controlled double crossover study of equivalent dose formulations of haloperidol and pimozide was conducted 22 patients randomly assigned to first one active drug treatment and then the other. Biweekly assessment and flexible dose titration mimicked clinical practice. The primary outcome variable was total score on the Tourette Syndrome Global Scale after 6 weeks of each treatment (placebo, pimozide, haloperidol), with a 2-week placebo baseline period and intervening 2-week placebo washout periods between treatments.

The clinical goal of 70% tic reduction was chosen for dose titration on the basis of outcome data from previous controlled studies. According to total scores on the Tourette Syndrome Global Scale, 64% (N=14) of the 22 subjects achieved this goal during either of the active treatments, compared to 23% (N=5) with placebo treatment. The mean effective doses of pimozide and haloperidol were equivalent: 3.4 mg/day (SD=1.6, range=1-6) and 3.5 mg/day (SD=2.2, range=1-8), respectively. In six of the seven patients who failed to meet the clinical tic reduction criteria, side effects precluded further dosage increases.

To evaluate treatment efficacy, an ANOVA on the primary tic outcome measure, the Tourette Syndrome Global Scale total score, was performed. This analysis revealed a treatment group effect. Scores on motor and vocal components of this subscale were as follows. With pimozide: mean=4.9 (SD= 3.4) for motor tics, mean=2.1 (SD=2.4) for vocal tics; with haloperidol: mean 5.1 (SD=4.8) for motor, mean= 3.7 (SD=5.5) for vocal; with placebo: mean=8.4 (SD= 5.7) for motor, mean 5.1 (SD=6.0) for vocal. An ANOVA on the secondary tic outcome measures of severity (CGI) and patient self-rated tics (Tourette's Syndrome Symptom List) also demonstrated a treatment group effect.

The CGI tic severity scale scores showed both pimozide (mean=3.1, SD=1.4) and haloperidol (mean= 3.1, SD=1.4) to be superior to placebo (mean=4.6, SD= 1.0) at the 1% level. Global assessment of functioning on the clinician-rated Children's Global Assessment Scale also revealed a treatment group effect: scores with both pimozide (mean=75.9, SD=16.6) and haloperidol (mean=73.6, SD=16.5) were significantly different from those with placebo (mean=66.4, SD=12.8). Behavioural outcomes for each treatment were evaluated with the Tourette's Syndrome Global Scale behavioural subscale and the Tourette Syndrome Symptom List selfrated behavioural scale. Neither behavioural scale showed a treatment effect.

General side effects (e.g., headache, stomachache, irritability) did not differ among treatments. Extrapyramidal symptoms, as measured by the Extrapyramidal Symptoms Rating Scale, demonstrated a decided treatment effect. The number of extrapyramidal symptoms in the haloperidol group (mean=4.1, SD=6.9) was higher in comparison with both the placebo group (mean=1.4, SD= 3.0) and the pimozide group (2.0, SD=3.0); with in haloperidol group, akathisia (N=2) and akinesia (N=2). At least 3 haloperidol- treated patients developed treatment-emergent depression or anxiety.

The authors concluded that in this study, at equivalent doses, pimozide was superior to haloperidol for controlling symptoms of Tourette's disorder in children and adolescents.

Assessor's comment:

The publications of Shapiro[14] (1989) and Borison[15] (1981) suggested efficacy of haloperidol in Tourette syndrome, however, both authors did not specify the number of children and adolescents included into the study and the dosage used in children and adolescents.

Connell[16] (1967) reported efficacy of haloperidol in only 4 adolescents.

The fourth double-blind placebo study (Salle[17], 1997) demonstrated poor efficacy of haloperidol in 22 children and adolescents with Gilles de la Tourette's syndrome compared to pimozide.

Comparator-controlled studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Shapiro E.[18] (1983)	Alternative treatment for patients refractory to HAL	Vs PZD		31 pts	19.6 y (10-50y)	HAL: 2-20 mg/d PZD: 2-48 mg/d		
Singer HS.[19] (1986)	To report experience with HAL, FPZ and CLO	Retro-spective study		120 pts (97/13)		HAL: 3.8mg/d (0.5-14mg)		
Li AY.[20] (2009)	Efficacy of integrative Chinese (Ningdong granule) and western medicine (HAL)	RD	6 months	90 pts HAL+Ng: 60 (46/14) HAL: 30 (24/6)	HAL+Ng: 9.59±3 y HAL: 9.6±2.95y	HAL	< 18y DSM-IV	YGTSS
Wu M.[21] (2009)	Efficacy of integrative Chinese medicine and western medicine (HAL)	RD, OL	12 weeks	82 pts		0.025 mg/kg twice daily		YGTSS

DB: double-blind; OL: OPEN LABEL, RD: randomised, PLA: placebo; HAL: haloperidol; PZD: pimozide; CLO: clonidine, FPZ: fluphenazine, TFZ: trifluoperazine, LI: lithium, DZP: diazepam, Ng: Ningdong granule, pts: patients
TS-SS: Tourette syndrome severity scale, CGI: Clinical Global Impression, TSGS: Tourette syndrome global scale, YGTSS: Yale Global Tic Severity Scale

The MAH provided the summary of Shapiro E.[18] (1983) publication. He conducted a controlled study in 31 patients (children, adolescents and adults) with TS and showed that pimozide was more efficacious and had less severe adverse effects than haloperidol. During treatment, the doses of haloperidol ranged from 2 to 20 mg/day and the doses of pimozide ranged from 2 to 48 mg/day. The mean (+SD) doses for 30 days during the last month of treatment were 5.4+3.4 mg/day for haloperidol (median, 4.0 mg/day; range, 1-14 mg/day) and 12.9+12.5 for pimozide (median, 8.0 mg/day; range, 1-64 mg/day).

Singer[19] (1986) reported his experience with haloperidol, fluphenazine and clonidine based upon a retrospective review of therapeutic experience in 120 patients enrolled in the Tourette syndrome clinic. In this population, 79 out of 120 patients (66%) required medications for the treatment of tics. Haloperidol therapy was used in 60 patients and as the initial drug in 55. This therapy was begun at a dose of 0.5 mg/day and increased weekly until tics were under control or significant side effects intervened. The average maximal dose of haloperidol was 3.8 mg/day (range: 0.5-14 mg). The average duration of haloperidol therapy was 25 months (range: 1 month to 9.8 years).
Thirty-one patients were treated with fluphenazine; for 6 it was the initial drug, for 18 the second, and for 7 the third drug. For fluphenazine, the standard initiating dose was 1 mg/day, the average maximal dose was 5.1 mg/day (range: 1-16 mg), and the average duration of therapy was 13 months (range: 1-47 months). Twenty-three patients, who had initially received unsuccessful therapy with haloperidol, were subsequently switched to fluphenazine.

Clonidine was administered to 30 patients in gradually increasing divided doses, beginning with 0.05 mg/day, 11 as the initial, 12 as the second and 7 as the third drug. The mean maximal dose was 0.4 mg/day (range: 0.1-0.8 mg) with a duration of 5 months (range: 1-44 months) of treatment.
Haloperidol was administered to 3 mild, 29 moderate, 16 moderately severe and 12 severe Tourette syndrome patients. The drug produced either good (32/60), fair (18/60) or poor (10/60) tic control, which corresponds to an overall improvement (good plus fair) rate of 83%. Side effects, however, were reported in 50 patients and were directly responsible for drug withdrawal in 20 patients. Major side effects noted in the 60 haloperidol-treated patients were: sedation (41), lethargy (17), irritability (4), dysphoria (22), personality change (14), appetite change (15), dystonia (2), and akathisia (7).
Thirty-one patients were treated with fluphenazine with a severity ranking as follows: 1 mild, 8 moderate, 9 moderately severe and 12 severe. Tic control during use of this drug was ranked as excellent (1/31), good (14/31), fair (10/31), or poor (6/31); an overall improvement (excellent, good of fair) rate of 81% was achieved. Six patients were withdrawn from fluphenazine because of uncontrollable side effects. Major side effects noted in the 31 fluphenazine-treated patients were: sedation (13), lethargy (1), irritability (2), dysphoria (2), personality change (4), appetite change (2), dystonia (1) and akathisia (1).
Twenty-three patients had received fluphenazine after a therapeutic trial with haloperidol. Patients No. 1-17 received fluphenazine immediately after haloperidol, whereas No. 18-23 had an intervening medication, usually clonidine, before receiving fluphenazine. In this subpopulation there were no significant differences between the ability of haloperidol or fluphenazine to control motor and vocal tic symptoms; 9 patients attained similar degrees of maximum control, 6 were better with fluphenazine and 8 were worse. In contrast, side effects occured significantly less often and were less severe when the individual was receiving fluphenazine.
Thirty patients received clonidine during the period of review. Ranking scales showed that 6 were classified as mild, 10 moderate, 5 moderately severe and 9 severe. The degree of control in these 30 patients was good (5/30), fair (9/30) and poor (16/30); an improvement (good plus fair) rate of 47% was achieved. Two individuals were withdrawn from clonidine because of unacceptable adverse effects (primarily sedation). The majority of responding patients were classified as having mild to moderate global severity rankings. Side effects were reported in 11: sedation (6), orthostatic hypotension (3), light-headedness (1) and irritability (2).
The authors concluded that the data also suggest that fluphenazine is an effective drug for tic suppression and produces fewer adverse effects than does haloperidol.

Li.[20] (2009) conducted a randomised comparator study to explore the clinical efficacy of integrative Chinese and Western medicine in treating Tourette's disorder. Ninety children (mean age treatment group: 9.59±3.00 y; control group: 9.60±2.95 y) with Tourette's disorder were randomized into two groups: the 60 patients in the treated group were treated by Ningdong Granule plus haloperidol, and the 30 in the control group treated by haloperidol alone. The course for both groups was 6 months. Conditions of the patients were estimated before and after treatment with Yale Global Tic Severity Scale (YGTSS), the short-term efficacy, adverse reaction of treatment were assessed at the end of treatment, and the long-term efficacy as well as the recurrent rate were evaluated half a year after the treatment was ended. Results showed that of the 60 patients in the treated group, the treatment on 36 was evaluated as remarkably effective, 21 as effective, and 3 as ineffective, the total effective rate being 95.0% (57/60), while of the 30 patients in the control group, the corresponding data were 9, 13, 8 and 73.3% (22/30), respectively, differences between groups in markedly effective rate and total effective rate were statistically significant.
The incidence of adverse reaction and the recurrent rate in the treated group were 13.3% (8/60) and 8.3% (5/60) respectively, all were lower than those in the control group, 36.7% (11/30) and

43.3 (13/30), showing statistical significances. Adverse events were drowsiness, lassitude, poor appetite, akathisia.
The authors concluded that integrative medical treatment (haloperidol + Ningdong Granule) on Tourette's disorder was markedly effective in clinical practice with less adverse reaction and lower recurrent rate then haloperidol alone.

Wu.[21] (2009) conducted a multicenter randomised parallel open-controlled study to assess the effect and adverse reaction of Qufeng Zhidong Recipe (QZR) in treating children's tic disorder (TD). The patients enrolled were assigned to two groups, 41 cases in the Chinese medicine (CM) group and 40 in the Western medicine (WM) group. They were treated by QZR and haloperidol (0.025 mg/kg twice daily) plus trihexyphenidyl respectively for 12 weeks as one course. In total, two courses of treatment were given. The curative effect and adverse reactions were evaluated by scoring with Yale Global Tic Severity Scale (YGTSS), Traditional Chinese Medicine Syndrome Scale (TCMSS), and Treatment Emergent Symptom Scale (TESS), as well as results of laboratory examinations. Results showed that after one course of treatment, the markedly effective rate in the CM and the WM group was 14.6% and 17.5%, respectively, and the total effective rate 43.9% and 47.5%, respectively, which showed insignificant difference between groups. However, after two courses of treatment, markedly effective rate in them was 73.2% and 7.5%, and the total effective rate was 100.0% and 57.5%, both showing significant differences between groups.
Besides, the adverse reactions occurred in the CM group was less than that in the WM group obviously (poor appetite, weight increase, hypopraxia, drowsiness).
The authors concluded that QZR has definite curative effect with no apparent adverse reaction in treating TD, and it can obviously improve the symptoms and signs and upgrade the quality of life and learning capacities in such patients.

Assessor's comment:
The comparator-controlled studies provided by the MAH are two studies (Shapirao[18], 1983 and Singer[19], 1986) without specification of number of children and adolescents, and 2 studies which compared the integrative Chinese medicine with the western medicine.

Open study

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments
Shapiro E.[22] (1973)	Review of 34 cases	Open-label	2 months to 5 years	21	19 y (8.6-64y)	6-180 mg/d acute treatment

PLA: placebo; HAL: haloperidol, pts: patients
TS-SS: Tourette syndrome severity scale, CGI: Clinical Global Impression, TSGS: Tourette syndrome global scale, YGTSS: Yale Global Tic Severity Scale

Shapiro.[22] (1973) evaluated the use of haloperidol in 34 patients with Tourette's syndrome. The median age was 19.0 years (range 8.6 to 64). Most of the patients were extensively treated before with many different types of psychotherapy, chemotherapy, and other therapeutic modalities without sustained success. The 21 patients included in the primary analysis fulfilled the following criteria: (1) on active treatment with haloperidol for more than one month; (2) followed instructions about dosage; (3) had no other complicating factors such as previous brain operation, prolonged remission, inadequate dosage; and (4) follow-up data were available for evaluation. Of the 34 patients, 13 did not meet the criteria outlined above and were not included

in the follow-up. The number of patients varied from 21 for the first two months to one at five years.
Most patients were treated by rapidly titrating the dosage of haloperidol in increments of 2 to 10 mg/day or week against an endpoint of symptom relief and the occurrence of incapacitating side effects. The dosage varied between 6 and 180 mg/day during acute treatment. This period lasted from one to three months before the dosage, effectiveness of the medicine, and side effects became stabilised. The dosage was then lowered against an endpoint of symptom relief and ability to tolerate side effects. Subsequently, for as long as one to four years, dosage was usually decreased to very small amounts with increased symptom relief.
After one year the median dosage was consistently 4 mg or lower. Above 2 mg of haloperidol, extrapyramidal side effects like akathisia, akinesia and parkinsonism usually required concomitant use of an anti-parkinsonian agent. Patients were evaluated by the senior author each month for the first nine months, at one year, and biyearly thereafter up to four years. The number of patients available during each of these evaluation periods varied from 21 for the first two months and trailed off to one patient at five years. At each evaluation period the dosage of haloperidol and the percent decrease of symptoms were recorded. The estimate of improvement was made by the clinician, family, and patient based on the overall percent decrease of symptoms that had occurred compared with the period prior to treatment. An estimate was made of the number of tics, vocalisations, coprolalia, etc, during a one-hour period for 24 hours prior to the onset of treatment. Results showed that at one year the median overall response to treatment was 90% or more decrease of symptoms with a dosage of 4 mg or less. The authors concluded that haloperidol was a difficult drug to use effectively. The dosage varied between 6 and 180 mg during acute treatment and had to be titrated against an endpoint of efficacy compared with side effects, but most patients were able to achieve over 90% decrease in their symptoms.

Assessor's conclusion on use of haloperidol in children with Tourette's disorder and tic disorder

The MAH provided 9 publications on the use of haloperidol in paediatric population with Tourette's disorder and Tic disorder. Four publications were placebo-controlled studies, 4 were active-comparator-controlled studies, and 1 was open-label study.
On the 9 publications, 4 studies were performed in children, adolescents and adults and the number of children and adolescents included are not specified, 2 were Chinese medicine comparator studies, and one study was open-label. Efficacy data are available in 26 children.
As data on adults, adolescents and children are pooled, no dosage estimation could be made.

Across studies, haloperidol treatment was associated with the following adverse effects:
Extrapyramidal symptoms (acute dystonia, akathisia, akinesia, hypopraxia), sedation/drowsiness, lethargy, depression, anxiety, orthostatic hypotension, light-headedness, irritability, lassitude, poor appetite, weight gain.
The most frequent adverse effects were Extrapyramidal symptoms and sedation.
Frequency of Extrapyramidal symptoms may be underestimated because of anticholinergic treatment frequently associated with haloperidol treatment.

These studies do not permit to conclude on efficacy of haloperidol in children and adolescents with Gilles de la Tourette's syndrome. Indeed, no recommendation of use of haloperidol in Tourette's disorder and tic disorder in children and adolescents could be made.

5.3 Use in the treatment of autistic disorder and atypical pervasive developmental disorders

The MAH provided 14 publications (13 studies) on use of haloperidol in paediatric population with autistic disorder and atypical pervasive developmental disorders. Seven publications were placebo-controlled studies, 2 were comparator-controlled studies, and 4 were open-label studies. (See tables below)

Placebo-controlled studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Campbell M.[23] (1978)	Efficacy of HAL in autistic children	DB, RD, vs PLA and BT	10 w	42/40 (32/8)	4.5 y (2.6-7.2 y)	0.5-4 mg/d		NIMH, CPRS, CBI, CGI, NGI, DOTES
Anderson LT.[24] (1984)	Efficacy of HAL	DB, RD vs PLA	12 w	40 (29/11)	4.58 y (2.33-6.92 y)	1.11 mg/d (0.5 to 3.0 mg/d)	DSM-III	CPRS, CGI, CPTQ
Anderson LT.[25] (1989)		DB, RD, cross-over vs PLA	14 w	45 (35/10)	4.49 y (2.02-7.58 y)	0.844mg/d (0.25 to 4 mg/d)	DSM-III	CPRS, CGI, CPTQ
Cohen IL.[26] (1980)		DB, cross-over vs PLA	-	15/10 (6/4)	4.7 y (2.1-7.0 y)		DSM-III	
Remington G.[27] (2001)	Comparison of CLOM and HAL	DB, RD, cross-over, vs CLOM and PLA	7 w	36 (30/6)	16.1 y (10-36y)	HAL: 1.3 mg/d (1-1.5 mg/d) CLOM: 128.4 mg (100-150)	DSM-IV	CARS, ABC, DOTES, ESRS
Perry R.[29,28] (1985)	To determine the prevalence of neuroleptic-induced dyskinesias	DB, RD, vs PLA	6 months	58 (47/11)	3.6-7.8 y	1.0 mg (0.5-3.0 mg/d)		BRS, TSRS, AIMS, AS, CPRS, CGI
Naruse H.[30] (1982)	Efficacy of PZD	DB, RD, cross-over vs PZD and PLA	8 weeks per treatment period	87	3-16 y		Children with behaviour disorder	QBC, RSABC

DB: double-blind; RD: randomised, BT: behaviour therapy; PLA: placebo; HAL: haloperidol; CLOM: clomipramine, pts: patients, PZD: pimozide
CPRS: Children's psychiatric rating scale, CBI: children behaviour inventory, CGI: clinical global impression, NGI: nurse global impression, DOTES: dosage record and treatment emergent symptoms, CPTQ: conners parent-teacher questionnaire; CARS: children autism rating scale, ABC: aberrant behaviour checklist, ESRS: extrapyramidal symptom rating scale; BRS: behavioural rating scale, TSRS: timed stereotypies rating scale, AIMS: abnormal involuntary movement scale, AS: abridged simpson, QBC: Questionnaire on Behavior in Children, RSABC: Rating Scale for Abnormal Behavior in Children

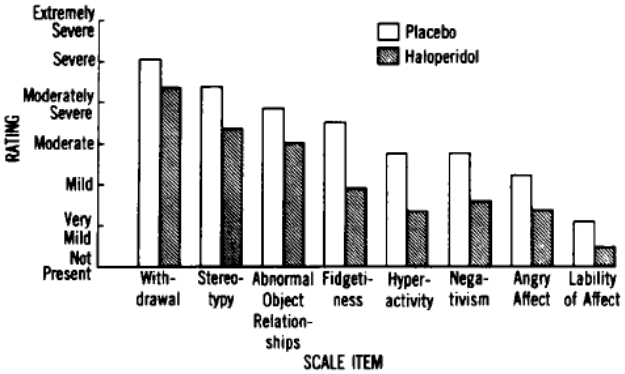
Campbell[23] (1978) assessed haloperidol and behaviour therapy, and the interaction of the two treatments with respect to their effects on symptoms and language acquisition in 40 autistic children aged 2.6 to 7.2 years. The study was placebo controlled and double-blind, using multiple independent raters who assessed treatment effects under three types of rating conditions.

Subjects were randomly assigned to the four treatment groups and were then maintained on placebo washout for 2 weeks. After this period, haloperidol or placebo was administered, starting with 0.5 mg in a single morning dose. Increments were done twice a week at regular intervals over a period of 3 weeks. Optimal dosage was determined on an individual basis for each child: No child received more than 4 mg of drug per day. Once the optimal dose was achieved, behaviour therapy was initiated and carried out for 7 weeks. During the last 2 weeks of behaviour therapy, every child was placed on placebo. No other psychoactive medication was

given to the child during the study. The mean haloperidol optimal dosage was 1.65 mg/d: the mean dosage was 0.07 and 0.15 mg/kg/d for children below and above 4.5 years respectively.
For children above 4.5 years of age, haloperidol was significantly superior to placebo in reducing the severity of withdrawal and stereotypy when measured in a highly structured environment.
The effects of repeated testing on symptomatology were apparent. As measured by the CBI, maladaptive behaviour was not normalised by haloperidol or language training.
The NGI revealed no effect due to drug, while the contingent reinforcement groups were rated superior to the noncontingent reinforcement groups. Performance of the sit-down instruction and imitative speech were facilitated by contingent reinforcement and not by drug. However, the combination of haloperidol and contingent reinforcement resulted in an acceleration in correct imitations, while a deceleration was apparent in the other groups. It is also noteworthy that verbal and nonverbal imitation covaried. This suggests that speech training might be facilitated by first firmly establishing the concept of imitation. In the present study, nonverbal imitation was not stressed. The most frequent adverse effect on haloperidol was excessive sedation, Extrapyramidal symptoms (2 acute dystonic reactions, one facial grimacing and hand mannerisms).

Anderson[24] (1984) conducted a double-blind placebo controlled study to evaluate the effects of haloperidol in 40 autistic children. Their ages ranged from 2.33 to 6.92 years (mean, 4.58 years). The children were randomly assigned to one of the two treatment sequences: haloperidol-placebo-haloperidol or placebo-haloperidol-placebo. Each treatment period lasted 4 weeks. Dosage was individually regulated until positive effects or untoward effects were seen. The starting dose was 0.5 mg/day; the maximum dose was 4.0 mg/day. Optimal doses of haloperidol for the 40 children ranged from 0.5 to 3.0 mg/day (mean, 1.11) and 0.019 to 0.217 mg/kg per day (mean, 0.05). For the 32 children who completed the learning part of the study, optimal doses ranged from 0.5 to 2.0 mg/day (mean, 1.11), which is 0.019 to 0.122 mg/kg per day (mean, 0.05).
According to the Children's Psychiatric Rating Scale, children receiving haloperidol showed statistically significant decreases in symptoms of withdrawal, stereotypies, hyperactivity, abnormal object relationships, fidgetiness, negativism, angry affect, and lability of affect (figure 1). According to the Clinical Global Impressions, haloperidol medication resulted in significantly lower ratings of severity of illness and greater behavioural improvement and drug efficacy across and within treatment periods.

FIGURE 1. Mean Scores of 40 Autistic Children Receiving Placebo or Haloperidol on Eight Items of the Children's Psychiatric Rating Scale



With haloperidol, the most frequent untoward effects above optimal doses or during the regulation period (with 0.5 to 4.0 mg/day) were excessive sedation and increased irritability. Acute dystonic reactions were observed in 11 children during dosage regulation, from 0.5 mg b.i.d. to 4.0 mg/day. With placebo, the most frequent untoward effects were increases in

hyperactivity, stereotypies, aggressiveness, impulsivity, and irritability and a decrease in attention span.

Anderson[25] (1989) conducted a double-blind and placebo-controlled clinical trial in autistic children that had three objectives: (a) to replicate earlier findings that haloperidol administration is associated with a significant reduction of behavioural symptoms; (b) to further assess its safety when given on a short-term basis: and (c) to assess whether it has an effect on discrimination learning. Forty-five children, 2.02 to 7.58 years old (M=4.49), were randomly assigned to one of three treatment groups (group I: HAL-PLA-HAL, group II: PLA-HAL-PLA, group III: PLA-PLA-HAL). There were 3 testing periods of 4-week duration. Thus, the entire study was of 14-week duration. Dosage level oh haloperidol was individually regulated; the starting dose was 0.5 mg/d. The dose of 4 mg/d was not to be exceeded. The therapeutic dose ranged from 0.25 to 4 mg/d (m=0.844mg/d), 0.016-0.184 mg/kg/d (m=0.047 mg/kg/d). Above therapeutic doses, excessive sedation and acute dystonic reaction were the most common side effect with haloperidol.
The main effect for haloperidol was significant for all three Children's Psychiatric rating Scale factors, the sum of all 14 CPRS items appropriate for autistic children, and for 7 individual scale items. For all CGI variables, inspection of means shows that all changes were in the direction of decreased symptoms during haloperidol treatment. The authors concluded that the results show that haloperidol is a powerful drug in reducing, both statistically and clinically, maladaptive behaviour in many autistic children who required pharmacotherapy. Under the condition of this study, haloperidol did not have generalised facilitating effects on discrimination learning.

Cohen IL[26] (1980) conducted a double-blind placebo-controlled within-subject reversal design to assess the therapeutic efficacy of haloperidol in a small sample (n=10) of preschool-age autistic children. Dosage was regulated individually, starting with 0.5 mg/d up to 4 mg/d; this occurred during the first week in order to determine the optimal dose for each child. The effect was more pronounced in the older children (4.5-7.0 y) and in those children who exhibited a high percentage of stereotypic behaviour at baseline. Haloperidol also facilitated the orienting reaction of the children to the request "look at me" with the effect more pronounced in the older children and those presenting with a low percentage of orienting on baseline. Stereotypy and orienting on baseline were negatively correlated. The untoward effects for patients on placebo consisted predominantly of worsening of pre-existing behavioural symptoms. Excessive sedation was apparent in 8 out of 10 of the children on doses of haloperidol above optimal, ranging from 1.0 mg/d to 4mg/d. Acute dystonic reactions occurred twice in 1 child, first at a dose of 1 mg bid and then again when the dose was lowered to 0.5 mg bid. The authors concluded that haloperidol is of therapeutic value as an adjunct to other psychosocial treatments and in parental management of autistic children. The present study indicated, however, that the immediate therapeutic effects would be most apparent in an older child who was very withdrawn and stereotypic.

Remington G[27] (2001) compared clopipramine, haloperidol and placebo in a double-blind, cross-over study. Thirty-six patients (10-36 years, mean 16.1y; number by age not specified), were randomly assigned to one of three treatment groups (CLOM-PLA-HAL, PLA-HAL-CLOM, HAL-CLOM-PLA). A 1-week washout was carried out before and between each arm of the treatment regimen. The duration of each trial was 7 weeks. For clomipramine, doses increases were as follows: 25 mg for 2 days, 25 mg twice a day for 2 days, 25 mg three times a day for 2 days, and 50 mg twice a day; thereafter, doses could be increased in 25-mg increments every 3 or 4 days on the basis of clinical assessment. For haloperidol, the dose increments were 0.25 mg at bedtime for 2 days, 0.25 mg twice a day for 2 days, 0.25 mg three times a day for 2 days, and

0.5 mg twice a day; thereafter, haloperidol doses were increased in 0.5 mg increments every 3 or 4 days as clinically indicated. Mean daily dose of haloperidol was 1.3 mg, range 1-1.5 mg.
There was statistically difference on the percentage of patients completing each trial: 69.7% (23/33) in haloperidol, 37.5% (12/32) in clomipramine; and 65.6% (21/32) in placebo group.
On the ABC a significant difference was found for Irritability, with post hoc comparisons indicating a significant difference between haloperidol, but not other groups, and baseline. Significance was also seen for Hyperactivity, and once again post hoc comparisons indicated a significant difference for haloperidol, but not other groups, versus baseline and placebo. No differences were detected for Stereotypic Behaviour, Lethargy, or Inappropriate Speech.
Table 2 summarizes results for the CARS, designed to evaluate severity of autistic symptomatology, and the two side effect scales, the DOTES and ESRS. A significant difference between groups and baseline was found on the CARS; post hoc comparisons indicated a significant difference between haloperidol and baseline.

TABLE 2. Comparison of placebo, clomipramine, and haloperidol with baseline for CARS, ESRS, and DOTES[a]

Measure	Baseline Mean (SD)	Placebo Mean (SD)	Clomipramine Mean (SD)	Haloperidol Mean (SD)	p
CARS	41.8 (7.1)	39.4 (7.0)	37.8 (8.7)	36.7 (6.1)	0.05[b]
ESRS	6.6 (6.7)	7.9 (7.1)	10.3 (7.3)	7.8 (5.8)	0.35[c]
DOTES	0.6 (2.2)	0.8 (1.7)	2.0 (2.9)	2.3 (3.3)	0.07[d]

[a]CARS, Childhood Autism Rating Scale; ESRS, Extrapyramidal Symptom Rating Scale; DOTES, Dosage Treatment Emergent Symptom Scale.
[b]Haloperidol versus baseline ($p < 0.05$).
[c]Results reported for Parkinsonism score, but nonsignificant for all ESRS measures.
[d]Results for Behavioral Toxicity subscale, but nonsignificant for all subscales.

The authors concluded that these results favour haloperidol over clomipramine in the treatment of autistic disorder. The two agents demonstrated comparable improvement when compared with baseline if there was a full therapeutic trial; however, significantly fewer individuals treated with clomipramine were able to do this, for reasons related both to side effects and efficacy. On a specific measure of stereotypy, clomipramine was not superior to haloperidol.

Perry R[28] (1985) designed a prospective study in autistic children most of whom have a high baseline rate of stereotypies to determine the actual prevalence of neuroleptic-induced dyskinesias in this population. Following two short-term double-blind and placebo-controlled studies of haloperidol (Anderson et al., 1984[24]; Campbell et al., unpublished data) those children who showed clinically significant improvement according to parents and hospital staff, were enrolled in this ongoing prospective longitudinal study. Improvements included decreases in stereotypies, withdrawal, hyperactivity, and aggressiveness.
58 children were randomly assigned in a double-blind fashion to continuous (7 days a week of haloperidol) and discontinuous (5 days a week of haloperidol and 2 days a week of placebo) administration of haloperidol, for periods of 6 months. Each 6-month treatment period was followed by a 4-week placebo period, in order to assess (a) whether further drug therapy is required to reduce the behavioural symptoms, and (b) whether withdrawal dyskinesias will emerge.
At the time of publication, 58 children, ages 3.6 to 7.8 y, received haloperidol over a period of time raging from 3.5 months and up to 42.5 months, cumulatively. The daily doses ranged from 0.5 to 3 mg/d (mean 1 mg) or 0.02-0.22 mg/kg (mean 0.05 mg/kg).
Thirteen children (22%), ages 4.1 to 7.8 years, developed mild to moderate drug-related abnormal movements after 3.5 and up to 42.5 months of cumulative treatment with haloperidol. Drug schedule (continuous vs. discontinuous) had no effect on the development of drug-related movements. In 4 children the onset of movements was during haloperidol administration and in 9 during placebo. In 11 children the movements were de novo, and in 2 children there was a change in pre-existing movements (stereotypies) only. Two of these 13 children developed both types of movements. The movements ceased within as few as 16 days but by 9 months in all

cases. In 10 children they remitted spontaneously, and in 3 children when haloperidol was reinstituted.

In a second publication, Perry R[29] (1989) followed the description of the precedent study (Perry R[28], 1985). Eighty-two children were enrolled in the study. Sixty completed the initial 6 months of haloperidol treatment. Their ages at entry into the study ranged from 2.3 to 7.9 years (M=5.1 years). Haloperidol doss ranged from 0.5 to 4.0 mg/day (M=1.23mg) or 0.016 to 0.209 mg/kg/day. Twelve children had haloperidol-related dyskinesias. Of these 12 children, three had dyskinesias while receiving haloperidol and nine had withdrawal dyskinesias during the placebo phases.
On the CPRS, the Autism Factor (five items of the CPRS: Fidgetiness, Withdrawal, Unspontaneous Relation to Examiner, Other Speech Deviances, and Stereotypies) and the sum of 14 selected items appropriate for autistic children were significantly reduced with long-term haloperidol treatment. The CGI Severity of Illness ratings were found to be reduced significantly after 6 months on haloperidol. The average CGI Global Improvement rating after 6 months was 2.74 (2 = much improved, 3 = minimally improved).
Using the Improvement rating scores, 56% of the subjects were much improved. Using a criterion of an improvement (decrease) in CGI Severity of Illness scores of 2 points or more, 24% of the subjects were much improved.
Of the 82 children who were enrolled in the study, 70 were randomly assigned to the continuous (N=36; 30 completed the 6-month treatment period) versus discontinuous (N=34; 22 completed the 6-month treatment period) haloperidol treatment schedule.
The authors concluded that when administered on a long-term basis, haloperidol remains effective in reducing a variety of maladaptive symptoms in autistic children, thus helping these severely disturbed young patients to remain in the community with their families and in special education programs. The therapeutic changes associated with haloperidol administration were both statistically and clinically significant. Discontinuous drug administration did not diminish drug efficacy in this study. There was no difference in side effects in the continuous group as compared to the discontinuous group. Peri et al[28] (1985) previously reported that this type of discontinuous haloperidol schedule (off medication 2 days/week) did not have a significant effect on tardive or withdrawal dyskinesias in this population.

Naruse H.[30] (1982) conducted a multicenter, double-blind crossover study of pimozide in comparison with haloperidol and a placebo in children with behavioural disorders (psychosis, neurosis, autistic disturbance, hyperkinetic syndrome, and mental retardation). 87 children, aged from 3 to 16 years, and had behavioural disorders who were difficult to treat with psychotherapy, were included. 34/87 children presented autistic disturbance. According to the dosage of treatment, a fixed-flexible method was applied using cross-over design. One tablet (pimozide 1 mg or haloperidol 0.75 mg) was given once in the evening. The maximum daily dose of respectively pimozide and haloperidol was restricted to 5mg and 3.75 mg for the age group of 3 to 5 years old, 6 mg and 4.5 mg for 6 to 11 and 9 mg and 6.75 mg for 12 to 16 years. In a crossover design of 3 drugs, there are 6 combinations with different order available. Duration of treatment period was 8 weeks. A 1-week washout period was recommended before the trial, but there was no washout period at switchover of drugs.
The authors and his study group have developed 2 efficacy scales used into this study: the Questionnaire on Behaviour in Children (QBC) for parents or guardians and the Rating Scale for Abnormal Behaviour in Children (RSABC) for therapists.
The results of the global preference were stratified according to the diagnosis. Pimozide as well as haloperidol were statistically significantly superior to the placebo in patients with autistic disturbance. Pimozide was significantly superior to placebo in each of the 3 RSABC clusters: "abnormal behaviour", "abnormal symptom" and "mental disorder" and in each of the 4

subclusters for the cluster "abnormal behaviour". Haloperidol was significantly superior to placebo in 2 of the 3 clusters, "abnormal behaviour" and "mental disorder". Pimozide was superior to placebo in 17 of the 49 factors, whereas haloperidol was superior to placebo in 11 of the 49 factors. There was no significant difference between pimozide and haloperidol.
Safety observation showed that both pimozide and haloperidol produced more sleepiness than the placebo. There was no significant difference between pimozide or haloperidol and placebo in frequency of other side-effects.
The authors concluded that particularly patients with autistic disturbance appear to benefit from both haloperidol and pimozide, as compared to the control treatment with no significant difference between the two drugs.

Assessor's comments:
The MAH provided 8 publications of placebo-controlled studies in autistic disorder. Most of them are in cross-over. These publications are old and clinical data provided are uncomplete. All are short-term studies except one 6-month study in which the objective was not efficacy but prevalence of neuroleptic-induced dyskinesias (Perry[28,29,] 1985). However, across placebo-controlled studies, significant decreases in behavioural and maladaptive symptoms such as withdrawal, stereotypies, hyperactivity, agressiveness were described.

Comparator studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Faretra G.[31] (1970)	Comparison of HAL and FPZ	DB, RD, vs FPZ	8 weeks	52	-	-	Disturbed children < 12 y	
Miral S.[32] (2008)	Comparison of RIS with HAL	DB, RD, vs RIS	12 weeks	30 (24/6)	8-18 y HAL: 10.9 y RIS: 10 y	0.01-0.08 mg/kg/d	AD as DSM-IV	RF-RLRS ABC, CGI-S, CGI-I

HAL: haloperidol, FPZ: fluphenazine; RIS: risperidone
DB: double-blind; RD: randomised, AD: autistic disorder
RF-RLRS: Ritvo-Freeman Real Life Rating Scale; ABC: Aberrant Behavior Checklist, CGI: Clinicla Global Impression scales; CGI-I: CGI- Improvement, CGI-S: CGI-Sverity

Faretra G.[31] (1970) conducted a double-blind, randomised study to compare the effectiveness of haloperidol and fluphenazine in disturbed children 12 years of age or younger. 52 children were included, 25 into haloperidol treatment group and 27 into fluphenazine treatment group. 87 % of them were childhood schizophrenics. Initially, each patient received 0.25 mg of haloperidol or fluphenazine three times daily. This dose could be increase with a maximum at 1.25 mg three times daily. Most of the children received the maximum dose for the last three weeks of the drug administration period. The comparison was based on the effectiveness of the drugs in reducing the severity of several target symptoms and symptom clusters and on the overall improvement of the children. The period of drug administration was eight weeks. In overall improvement both drugs were similar in effectiveness, slightly more than half the patients in each drug group showing improvement. In reduction of target symptoms, there were some differences between the drugs. Both drugs effectively reduced anxiety, but haloperidol appeared to be more effective in reducing provocativeness and autism. In the social and motor behaviour type symptoms, haloperidol appeared to act more quickly, significant change in these occurring by four weeks with haloperidol but until eight weeks with fluphenazine. Side effects were mainly extrapyramidal.

Miral S.[32] (2008) conducted a double-blind, randomised, 12-week study to compare efficacy and safety of risperidone with haloperidol in the treatment of Autistic Disorder. 30 patients were randomised to received risperidone or haloperidol initiated at a dosage of 0.01 mg/kg/d and increased to 0.04 mg/kg/d until the end of the first 2 weeks. If tolerated, then it was increased to a maximum dosage of 0.08 mg/kg/d. 28 patients completed the study, 2 patients into the risperidone group withdrawn because of lack of efficacy. Dosages in the haloperidol group (n = 15) ranged from 1.0 to 5.7 mg/day (mean = 2.6 ± 1.3 mg/day), and those in the risperidone group (n = 13) ranged from 1.2 to 4.0 mg/day (mean = 2.6 ± 0.8 mg/day).
The risperidone group showed changes from baseline to end-point in all RF-RLRS subscale score (sensory-motor and social, affect, sensory, and language). The haloperidol group improved significantly in the first four subscales (sensory-motor and social, affect and sensory), but did not show significant improvement in the language subscale scores. The changes from baseline to end-point in ABC scores for both groups were significant. Of the two groups, those patients receiving risperidone saw a significantly greater improvement in their scores (P = 0.0063). The changes in baseline to end-point in Turgay DSM-IV scores were significant for both groups. Between the two groups, those patients receiving risperidone resulted in a greater improvement in scores (P = 0.0052). At end-point, according to the CGI-I scores, 2 (15.4%) of the risperidone patients had markedly improved, 9 (69.2%) had moderately improved, and 2 (15.4%) had slightly improved. In the haloperidol group, 9 (60.0%) had moderately improved, five (33.3%) had slightly improved, and one (6.7%) had shown no change. The CGI improvement scores were not significantly different between the two study groups at end-point.

Table 2 Scale scores end-point baseline comparison for each study group

	Risperidone		Haloperidol	
	Mean ± (SD)	*P*	Mean ± (SD)	*P*
Ritvo–Freeman Real Life Rating Scale				
Social				
Baseline	0.62 ± 0.50	**0.0032**	0.50 ± 0.41	**0.0113**
Endpoint	−0.11 ± 0.38		0.02 ± 0.57	
Sensory motor				
Baseline	0.90 ± 0.52	**0.0032**	0.69 ± 0.47	0.2075
End-point	0.36 ± 0.34		0.50 ± 0.44	
Affect				
Baseline	1.09 ± 0.41	**0.0072**	1.05 ± 0.61	**0.0296**
End-point	0.54 ± 0.34		0.64 ± 0.48	
Sensory				
Baseline	0.98 ± 0.46	**0.0118**	0.86 ± 0.44	**0.0046**
End-point	0.51 ± 0.25		0.58 ± 0.49	
Language				
Baseline	0.52 ± 0.37	**0.0044**	0.15 ± 0.44	0.0546
End-point	0.04 ± 0.25		−0.05 ± 0.5	
Aberrant Behavior Checklist				
Baseline	85.6 ± 27.3	**0.0022**	67.1 ± 25.1	**0.0037**
End-point	36.8 ± 13.8		45.8 ± 20.2	
Chouinard Extrapyramidal Symptoms Rating Scale				
Section I				
Baseline	0.23 ± 0.60	0.3173	0.33 ± 0.82	**0.0477**
End-point	0.15 ± 0.38		1.27 ± 1.75	
Parkinsonism				
Baseline	0.00	1	0.00	1
End-point	0.00		0.00	
Dystonia				
Baseline	0.00	1	0.00	1
End-point	0.00		0.00	
Dyskinesia				
Baseline	0.00	0.3173	0.40 ± 1.55	1
End-point	0.08 ± 0.28		0.13 ± 0.30	
Turgay DSM-IV Scores				
Baseline	91.5 ± 20.1	**0.0019**	77.6 ± 23.1	**0.0012**
End-point	53.5 ± 9.6		59.6 ± 21.3	

* Wilcoxon tests results. Results significant at $P < 0.05$ are shown in bold

Table 3 Comparison of risperidone and haloperidol groups at end-point ($n = 30$)

Rating scales	*P*-values*
Ritvo–Freeman Real Life Rating Scale	
Sensory-motor	0.0977
Social	0.2539
Affect	0.5551
Sensory	0.2539
Language	0.0799
Aberrant Behavior Checklist	**0.0063**
Turgay DSM-IV	**0.0052**
Chouinard Extrapyramidal Symptoms Rating Scale	
Section I	0.1696
Parkinsonism	0.7856
Dystonia	1.0000
Dyskinesia	1.0000
Clinical Global Impression	
Degree of improvement	0.1184
Therapeutic effectiveness	0.1184
Side-effects	0.1423
CGI global	0.6500

*Mann–Whitney U test. Results significant at $P < 0.05$ are shown in bold; *P*-values

The authors concluded that in their study, risperidone and haloperidol had comparable outcomes on the CGI and on the RF-RLRS sensory, social, and affect subscales. Nevertheless, risperidone was found to be superior to haloperidol on the RF-RLRS sensorymotor and language subscale, ABC, and Turgay DSM-IV scales.
Children treated with haloperidol had a worsening of EPS or the development of EPS during the trial. The others adverse events in haloperidol group were constipation, enuresis nocturna, blunted affect, rigidity, difficulty sleeping, and upper respiratory tract infection.

Assesor's comments:
The MAH sumitted 2 publications with comparator-controlled studies.
The first publication (Faretra G.[31], 1970) included disturbed children. The second publication is a recent one (Miral S.[32], 2008) which compare risperidone and haloperidol without placebo-arm in the treatment of autistic disorder in 30 children. Results indicated that risperidone and haloperidol had comparable outcomes on the CGI and on the RF-RLRS sensory, social, and affect subscales. Nevertheless, risperidone was found to be superior to haloperidol on ABC.

Open studies

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Joshi P[33] (1988)	Therapeutic effects of low dose neuroleptic treatment	OL, vs FPZ		12 (10/2)	9.1 y (7-11 y)	0.04 mg/kg/d	Pervasive developmental disorder as DSM-III	Behaviour HCBS CBC
Hoshino Y[34] (?)		OL		60		0.015-0.10 mg/kg/d		
Malone RP[35] (2001)	Efficacy of OZP	OL, RD, vs OZP	6 w	12 (8/4)	7.8 y (4.8-11.8 y)	1.4 ± 0.7 mg/d	Pervasive developmental disorder as DSM-IV	CGI, CPRS
Gencer O[36] (2008)	Efficacy of RIS	OL, vs RIS	12 w	28	8-18 y	0.01-0.08 mg/kg/d	Autistic disorder as DSM-IV	CGI, CPRS, RF-RLRS, ABC, TPDDRS

HAL: haloperidol, FPZ: fluphenazine; RIS: risperidone , OZP: olanzapine, RIS: risperidone
DB: double-blind; RD: randomised, AD: autistic disorder
HCBS: Hopkins child behavioural score, CBC: Conners Behaviour Checklist, RF-RLRS: Ritvo-Freeman Real Life Rating Scale; ABC: Aberrant Behaviour Checklist, CGI: Clinical Global Impression scales; CGI-I: CGI- Improvement, CGI-S: CGI-Severity, TPDDRS: Turgay DSM-IV pervasive developmental disorder rating scale

Joshi P[33] (1988) administered in an open manner fluphenazine or haloperidol to 12 children aged 7 to 11 years. Eight satisfied DSM-III criteria for childhood-onset pervasive developmental disorder, and the remaining four satisfied criteria for atypical pervasive developmental disorder.
On the basis of clinical assessment of response, the optimal mean ± SD doses of haloperidol and fluphenazine were 0.04±0.01 mg/kg/d or 1.3±0.7 mg/day, respectively.
From our series of 12 inpatients in an open study, clinical observations and rating scale assessments indicate remarkable improvement in peer interactions, reduction in autistic-like behaviours, improved reality testing, and decrements in impulsivity and hyperactivity with low-dose neuroleptic treatment. Preoccupation with fantasies and morbid interests as well as

resistance to change with perseveration appeared to be considerably reduced, as supported by follow-up projective testing in five of the 12 patients. Two children experienced mild Extrapyramidal symptoms with rigidity and cogwheeling.

Hoshino Y[34] used small doses of haloperidol in treating autistic children (39 cases of autism and 21 cases of autistic oligophrenia). The dose of haloperidol was 0.015-0.10 mg/kg/day). The authors found that this dose was sufficient in the therapy of autistic children and a larger dose could cause side effects such as drowsiness and extrapyramidal symptoms. Results showed that: 1) out of 39 cases of autism, 25 cases (64%) showed improvement and out of 21 cases of autistic oligophrenia, 12 cases (57%) showed improvement; and 2) the symptoms where haloperidol was most effective were “increased psychomotor activity,” “poor concentration”, “poor responsiveness,” “poor relationships with adults or children”, “affect disturbance” and “low level of verbal productions” in accordance with the results of Children’s Psychiatric Rating Scale. The main side effects from small doses of haloperidol were drowsiness, increased salivation, anorexia and diarrhoea. These side effects were slight and temporary and disappeared soon after the reduction of drug dosage. Serum serotonin levels were measured before drug administration and two weeks afterwards. Of eight cases of autism, six showed an increase and two a decrease after the administration, but there were no statistically significant differences.

Malone RP[35] (2001) evaluated the efficacy and safety of open-label olanzapine as a treatment for children with autistic disorder by using haloperidol as a standard comparator treatment. 13 patients of whom 12 children with DSM-IV autistic disorder (mean age 7.8 ± 2.1 years) were randomized to 6 weeks of open treatment with olanzapine or haloperidol. The starting dosage of haloperidol was 0.25 mg/day for subjects who weighed 40 kg or less and 0.5 mg for subjects who weighed more than 40 kg. In general, dosages could be increased as clinically indicated in 0.5 mg increments up to 1 mg a week, as needed. The maximum dosage for haloperidol permitted by the study protocol was 5 mg/day. Mean final dosages were 7.9 ± 2.5 mg/day for olanzapine and 1.4 + 0.7 mg/day for haloperidol.
Outcome measures included the Clinical Global Impressions (CGI) and the Children’s Psychiatric Rating Scale (CPRS). Results showed that both groups had symptom reduction. Five of six in the olanzapine group and three of six in the haloperidol group were rated as responders according to the CGI Improvement item. Subjects showed improvement on the CPRS Autism Factor. Side effects included drowsiness and weight gain. Results showed that olanzapine and haloperidol had a comparable outcome on both the CGI and the CPRS. The authors concluded that the findings suggested that olanzapine is a promising treatment for children with autistic disorder and that further placebo-controlled and long-term studies of olanzapine in autistic disorder are required.

Gencer O[36] (2008) conducted a long-term open-label continuation study of the randomised, double-blind, controlled trial of risperidone and haloperidol study for 12 week in autistic children and adolescents (Miral S.[32]; 2008). A total of 28 subjects between 8 and 18 ages with autistic disorder were enrolled to the 12-week, open label continuation phase of the study. In this study patients received the same titration of the same medication than one received during the first 12-week double-blind treatment period. Medication dosage ranged from 1.0 to 6.0 mg/day (mean = 2.7±1.3 mg/day) in the haloperidol group (n=15), and 1.2-3.8 mg/day (mean = 2.5 ± 0.7 mg/ day) in the risperidone group (n=13) in the open label continuation study.
Results indicated that degree of improvement on CGI was superior in the risperidone group compared to the haloperidol group at week 24.
The change in RF-RLRS sensory-motor subscale scores between the baseline and week 24 was statistically significant in the risperidone group but not in the haloperidol group. The mean values of RF-RLRS language subscale scores showed a significant increase at week 24 from baseline in the haloperidol group (i.e. deterioration).

The change from baseline risperidone group was significant at week 24; but was not significant in the haloperidol group. The changes of ABC scores were not significantly different between the two study groups at week 24. The difference between the baseline and week 24 TPDDRS scores was statistically significant both in the risperidone and haloperidol group. Three patients received anticholinergic agents because of EPS. Weight gain was observed more frequently in haloperidol group. Serum prolactin levels were significantly high in the haloperidol group at the end. Other reported side events were constipation, enuresis nocturna, blunt effect, difficulty sleeping, increased appetite and upper respiratory tract infection.

Assessor's conclusion on use of haloperidol in the treatment of autistic disorder and atypical pervasive developmental disorders

The MAH provided 14 publications (13 studies), of which 7 placebo-controlled studies, 2 comparator-controlled studies, and 4 open-label studies. These publications are old and clinical data provided are incomplete. All studies are sort-term design except one 6-month study in which the objective was not efficacy but prevalence of neuroleptic-induced dyskinesia.

However, across studies, significant decreases in behavioural and maladaptive symptoms as withdrawal, stereotypy, hyperactivity, agressiveness were frequently described. Furthermore, results of one recent study (Miral S.[32], 2008) which compared risperidone and haloperidol in the treatment of autistic disorder, indicated that risperidone and haloperidol had comparable outcomes on the CGI and on the RF-RLRS sensory, social, and affect subscales. Nevertheless, risperidone was found to be superior to haloperidol on ABC.

The majority of studies included children aged around from 2 to 11 years old.
All across studies, the dosage in children and adolescents ranged from 0.01 to 0.22 mg/kg/d when dosages were stated per weight and from 0.25 mg/d to 6.75 mg/d when dosages were not stated per weight. Haloperidol was always initiated according to a dosage schedule with the initial dose being 0.25 mg or 0.50 mg/d. The maximal daily dose was often 4 mg/d for patients. One study stratified the maximum authorised daily dose by age range (Narus[30], 1982) as follow: 3.75 mg for 3-5 years, 4.5 mg for 6-11 years, and 6.75 mg for 12-16 years.

Across studies, haloperidol treatment was associated with the following adverse effects:
Extrapyramidal symptoms (acute dystonic reactions, one facial grimacing and hand mannerisms, abnormal movements, rigidity, cogwheeling, increased salivation), excessive sedation/sleepiness/drowsiness, increased irritability, constipation, enuresis nocturna, blunted affect, difficulty sleeping, upper respiratory tract infection, anorexia, diarrhoea, weight gain, serum prolactin level increase.
The most frequent adverse effects observed were Extrapyramidal symptoms and sedation.
Frequency of Extrapyramidal symptoms may be underestimated because of anticholinergic treatment frequently associated with haloperidol treatment.

Based on these data, no recommendation on use of haloperidol in the treatment of autistic disorder and atypical pervasive developmental disorders could be made. However, these data provided some evidence of efficacy on behavioural symptoms. This should be developed by the MAH in a global analysis of the use of haloperidol in treatment of behavioural symptoms in children and adolescents with pervasive developmental disorder or conduct disorder.

5.4 Use in aggressiveness

The MAH provided two publications: one published and one unpublished.

Published

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Campbell M[37] (1984)	Efficacy of HAL and Li	DB, RD, vs PLA	4 w	61 (57/4)	(5.2-12.9 y)	HAL: 2.95 mg/d (1.0-6.0 mg/d) Li: 1,166 mg/d (500-2,000)	Treatment-resistant hospitalized aggressive children with CD	CPRS, CGI CPTQ

DB: double-blind, RD: randomised, PLA: placebo, HAL: haloperidol, Li: lithium,
CD: conduct disorders, CPRS: Children's Psychiatric Rating Scale, CGI: Clinical Global Impression, CPTQ: conners parent-teacher questionnaire

Campbell M[37] (1984) assessed the efficacy and safety of haloperidol and lithium in inpatients with the diagnosis of conduct disorder with a behavioural profile of aggressiveness and explosiveness. The study was randomised, double-blind, 4-week, placebo-controlled.
Haloperidol dosage began at 1.0 mg/day; increments were gradual during a period of two weeks until a maximum dose of 16.0 mg/day was reached or until the development of untoward effects required reduction or stabilisation of dosage. Lithium carbonate dosage began at 250 mg/day; increments were made similarly. The maximum dosage of lithium carbonate was not to exceed 2,000 mg/day and/or a blood level of 1.8 mEq/L. Dosage was individually regulated during a period of two weeks, which was followed by a two-week period of optimal dosage. The optimal dosage for children who received haloperidol ranged from 1.0 to 6.0 mg/day (mean, 2.95 mg/day), or 0.04 to 0.21 mg/kg/day (mean, 0.096 mg/kg/day). The maximum dosage given during the regulation period ranged from 1.5 to 12.0 mg/day. The optimal dosage for children who received lithium carbonate ranged from 500 to 2,000 mg/day (mean, 1,166 mg/day). With these doses, the lithium level in serum ranged from 0.32 to 1.51 mEq/L (mean, 0.993 mEq/L). 61 children completed the study. Results showed that both haloperidol and lithium were superior to placebo in ameliorating behavioural symptoms on CPRS and CGI. The hyperactivity, aggression, and hostility clusters were significant (figure 1). The authors reported that, at optimal doses, the untoward effects of haloperidol appeared to interfere more significantly with the children's daily routines than did those of lithium.

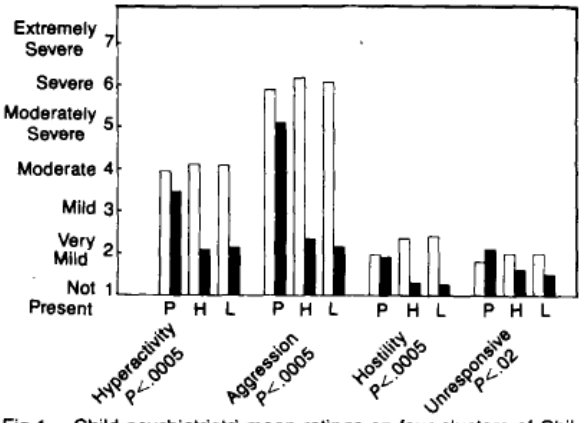


Fig 1.—Child psychiatrists' mean ratings on four clusters of Children's Psychiatric Rating Scale, before (white bars) and after (shaded bars) treatment. P indicates placebo; H, haloperidol; L, lithium carbonate.

The most common side effects in haloperidol group were excessive sedation, acute dystonic reactions, tremor, and drooling.

Unpublished

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Harris DP[38] (?)	Pilot project	OL, cross-over vs CPZ	-	7	7-14 y	-	-	-

OL: open label, CPZ: chlorpromazine

Harris [38] conducted an open-label study to evaluate the use of haloperidol in children who showed more aggression then the psychiatric unit could reasonably handle. Seven children in the age range from 7-14 years were included in the study. Each child served as his own control and received first chlorpromazine and was then changed to haloperidol. The design called for a period of initial observation without medication and another wash-out period of at least one week between the two drugs. However, this was not possible, as the ward found it impossible to work with these severely disturbed children without medication. The dosage of haloperidol was increased very slowly, starting at 0.25mg daily, and proceeding by increments of 0.25 mg/day until very high dosages of 10-12 mg/day were reached. Results showed no differences between the two drugs and the authors found in this study no noticeable therapeutic effect on aggressiveness either with chlorpromazine or large doses of haloperidol. Liver function tests, white blood cell counts and differential counts were monitored during the period on both drugs and no signs of toxicity were found. Extrapyramidal effects were controlled by Cogentin 1-2 mg daily and in no case was drug therapy interrupted because of these drugs.

Assessor's comment:
The MAH provided one published well-design study and one unpublished open-label study in agressiveness.
The first study was conducted in 61 children with conduct disorder randomised into 3 treatment groups. High doses of haloperidol were used: the maximum dosage given during the regulation period ranged from 1.5 to 12 mg/d. Results showed statistically significant improvement on aggression, hyperactivity and hostility of Children's Psychiatric Rating Scale.
In the 2 studies, haloperidol treatment was associated with the following adverse events: Extrapyramidal symptoms, acute dystonic reactions, tremor, excessive sedation, and drooling.

These data should be developed by the MAH in a global analysis of the use of haloperidol in treatment of behavioural symptoms in children and adolescents with pervasive developmental disorder or conduct disorder.

5.5 Use in Attention deficit hyperactivity disorder (ADHD)

The MAH presented a single study in this indication not listed in any of the EU SmPCs. The MAH stated that it is presented as an example of clinical experience.

Placebo controlled study

First	Study	Design	Duration	Subjs by	Mean	Treatments	Diagnosis

author Date	Objective			arm entered/ compl M/F	Age		Incl. criteria
Werry J[39] (1975)	Cognitive effect comparison	DB, cross-over, vs MPD and PLA	12 w	24 (20/4)	7.75 y (4-12 y)	MPD: 0.3mg/kg HAL: 0.025 and 0.05 mg/kg	severe hyperactivity or aggressive behaviour associated with hyperactivity

DB: double-blind, PLA: placebo, MPD: methylphenidate

Werry J[39] (1975) conducted a double-blind placebo controlled crossover (within subject) study. 24 children (4-12y) with severe hyperactivity or aggressive behaviour associated with hyperactivity received each of four drug conditions (placebo, methylphenidate hydrochloride [0.3 mg/kg], a low dose of haloperidol [0.025 mg/kg], and a high dose of haloperidol [0.050 mg/kg]) for three weeks, for a total of 12 weeks with two-day wash-out between phases.
The data suggested that methylphenidate and low-dose haloperidol, although to a lesser degree, improved these cognitive functions, whereas high dose haloperidol appeared to cause them to deteriorate. The author stated that the clinical importance of this biphasic effect was that it was the dose of haloperidol, not the drug itself, that may cause cognitive impairment. Based on this study, most children and adolescents treated for ADHD with haloperidol should receive doses between 0.5 and 2.0 mg/day (i.e., 0.025 mg/kg for a weight range of 20 to 80 kg).

Assessor's comment:
According to this single study with small number of children, no recommendation can be made on the use of haloperidol in ADHD.

5.6 Use in anxiety-tension states

The MAH presented a single study in this indication not listed in any of the EU SmPCs. The MAH stated that it is presented as an example of clinical experience.

Open study

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Gilbert MM[40] (1969)	Efficacy of HAL	OL	1 to 8 w	37 pts	36 y (7-79 y)	ID: 2 mg (0.75-3.0 mg MD: 1 mg (0.50-1.5 mg)	Anxiety-tension reaction	Global improvement Target symptoms

OL: open-label, HAL: haloperidol, ID: initial dose, MD: maintenance dose

Gilbert MM[40] (1969) evaluated the effectiveness of haloperidol in 37 patients (32 adults and 5 children and adolescents) presenting various symptoms of anxiety-tension states. Over two-thirds of the patients were between 20 and 50 years old (M=36 y; 7-79 y). The usual starting dose of haloperidol was 0.75 mg and then, adjusted according to response. In children and adolescents, the range of initial doses (average) used was 0.75-3.0 mg (2 mg) and the range of maintenance doses (average) was 0.50-1.5 mg (1 mg). Duration of treatment varied from one to 8 weeks. Over three-fourths of the patients, including all five of the children and adolescents, showed good (29%) to excellent (48.4%) global improvement. 19.4 % of the patients showed poor improvement and 3.2 % fair improvement. Reduction occurred in the severity of all target

symptoms (tension, irritability, anxiety, and agitation, fatigue, lethargy, fear) and was statistically significant for tension, irritability, anxiety, and agitation. A total of eight types of adverse reactions were noted in 11 of the adult patients. None of the children or adolescents exhibited adverse reactions.

Assessor's comment:
According to this single open-label study in 5 children and adolescents, no recommendation can be made on the use of haloperidol in anxiety-tension states.

5.7 Use in emotionally disturbed children with heterogeneous diagnoses

The MAH provided one placebo-controlled study, one comparator study and two open-label studies.

Placebo controlled study

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Lucas A[41] (1969)	Psychoactive drugs in the treatment of emotionally disturbed children	DB cross-over vs PLA	9-10 w	15 (14/1)	12.4 y (8.5-15.5 y)	-	Responders to phenothiazine drug	Behaviour

PLA: placebo, DB: double-blind

Lucas A[41] (1969) conducted a double-blind placebo-controlled crossover study of haloperidol in 15 significantly emotionally disturbed subjects from an inpatient unit. The children selected for this study were those presenting symptoms which in the investigator's experience responded favourably to phenothiazine drugs, namely: anxiety and tension, hyperexcitability, oppositional behaviour, aggressiveness and impulsiveness. The diagnoses were: Psychoneurosis (4), Brain Damage (3), Schizophrenia (3), Personality Disorder (3), Psychopathy (Affectionless) (2). Age range was 8.5 to 15.5 years with a mean age of 12.4 years. The placebo-controlled crossover, double-blind method of drug and placebo administration was used, with each child acting as his own control. The study itself was divided into three periods: (1) determination of dose with known active drug (one to two weeks); (2) treatment with either drug or placebo; and (3) the reverse of (2). Phases 2 and 3 each lasted for four weeks. Drug response was judged on the basis of ten behavioural characteristics which were rated daily on a six-point scale. These included: hyperactivity, anxiety and tension, oppositional behaviour (negativism), aggressiveness, impulsivity, relationship to peers, relationship to adults (staff), need for limit setting, response to limit setting, and participation in the program. Drug dosage was begun at a level of 0.5 mg daily and raised by 0.5 mg increments per day until either therapeutic response or excessive side effects were encountered. The maintenance dose was then established and continued for the duration of the study. Ten patients completed the study. For three of the behavioural categories (oppositional behaviour, relationship to peers, and response to limit setting) behaviour was significantly improved during drug administration as compared to placebo. The investigators decided to review the results in another way. The two psychiatrists supervising the study reviewed the individual records of the children and made a global rating of clinical change comparing previous drug administration, placebo and haloperidol. It was possible thus to rate 13 of the children. Of these 8 functioned better with haloperidol than placebo, and in

5 no difference could be noted. Drowsiness and lethargy were commonly encountered at effective dosage levels, and in 8 of the 15 patients they were prominent features. Slurred speech and increased salivation were noted in 4 patients. Four experienced nausea, and 3 increased muscle tonus. One patient had a tremor of the hands. Some developed a severe parkinsonian syndrome, but 3 required treatment with benztropine. In 2 patients, flushing of the face was noted, and blurring of vision and diplopia occurred in one.

Comparator study

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Ucer E[42] (1969)	Comparison of HAL with TDZ in emotionally disturbed, mentally retarded children	DB, RD, vs TDZ	8 w	50	9.7 y (7-12 y)	HAL: 2.25 mg TDZ: 52.99 mg	Chronic brain syndrome	Severity of symptoms

DB: double-blind, RD: randomised, TDZ: thioridazine

Ucer E[42] (1969) conducted a double-blind comparator study in 50 emotionally disturbed, hospitalised children, ages between 7 and 12, whose IQs ranged from 40 to 70. Twenty-six children (12 males and 14 females) received haloperidol and twentyfour (12 males and 12 females) received thioridazine. The diagnoses for the children were Chronic brain syndrome with behavioural disorder (20 on haloperidol, 19 on thioridazine), Psychoneurosis (3 on haloperidol, 1 on thioridazine), Schizophrenia (1 on haloperidol, 2 on thioridazine), and Personality disturbance (2 on haloperidol, 2 on thioridazine). The symptoms most commonly exhibited by the patients were anxiety, hostility, hyperactivity, aggressiveness, withdrawal, and impulsiveness. The severity of these symptoms was rated numerically on a scale of 0 for absent, 1 for mild, 2 for moderate, and 3 for severe. Initial daily dosages were 0.75 mg of haloperidol or 13 mg of thioridazine. The dosage was increased by one capsule (i.e. 0.25 mg of haloperidol or 5 mg of thioridazine) every 3 days until a daily dosage of 3.75 mg of haloperidol or 75 mg of thioridazine was reached. After a week on the maximum dose, the dosage was lowered to a maintenance level. In the haloperidol group, the mean daily dosage was 2.25 mg, and in the thioridazine group it was 52.99 mg.

A comparison of global improvement (based on improvement in general behaviour and symptom reduction) in the two drug groups showed that 54 per cent of the haloperidol group and only 21 per cent of the thioridazine group showed marked or moderate improvement. The larger percent age of improvement observed in the haloperidol group was statistically significant. The severity of hyperactivity, anxiety, aggressiveness, and impulsiveness was more significantly reduced by haloperidol than by thioridazine. Neither drug effected a significant improvement in withdrawal or hostility. Fifteen of the twenty-six haloperidol patients experienced thirty-one side effects. Four haloperidol patients dropped from the study after exhibiting limiting side effects: 3 cases of ataxia and one case of nausea and vomiting.

Open study

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments
Ayd FJ[43] (1969)	Efficacy of HAL	OL	3 months 1 year	18 (10/8)	12-18y	4 mg (2-10 mg)
Le Vann LJ[44] (1969)	Efficacy of HAL	OL vs PLA	2-82 days	100		3 and 3.1 mg

OL: open-label

Ayd[43] (1969) treated 18 adolescents (10 girls and 8 boys, ages 12 to 18 years) with haloperidol for three months to one year with daily doses ranging from 2 mg to 10 mg (average 4 mg). In this group there were 2 acute schizophrenics, 2 chronic schizophrenics, 8 anxious psychoneurotics with acting-out behaviour, 4 patients with hyperkinetic behaviour disorder, and 2 sociopaths. All had been treated previously for a minimum of two months with adequate doses of a potent phenothiazine, such as perphenazine, trifluoperazine, and fluphenazine, without satisfactory symptomatic improvement. Each patient served as his own control and after three months of haloperidol therapy each was assessed. This revealed: 1) no improvement in the two sociopaths and one chronic schizophrenic; 2) moderate improvement, i.e., at least a 50% reduction in the severity of target symptoms, in 8 patients (1 acute and 1 chronic schizophrenic, 4 anxious psychoneurotics, and 2 patients with hyperkinetic behaviour disorder); and 3) marked improvement or at least 75% reduction in the severity of target symptoms in 7 patients (1 acute schizophrenic, 4 anxious psychoneurotics and 2 patients with hyperkinetic behaviour disorder). Although none of the patients was completely rid of symptoms, the author concluded that haloperidol, rationally prescribed, could lessen disability and help to rehabilitate but would not provide a cure. Haloperidol treatment was associated with various Extrapyramidal reactions, depression, lethargy/fatigue, endogenous depression (early awakening, morning retardation, self-reproachfulness, and a depressed mood).

Le Vann LJ[44] (1969) administered haloperidol in an open study to 100 hospitalised psychiatric patients (61 males and 39 females). Fifty-three of the patients were children (12 years of age or under) and 47 were adolescents (over 12 years of age). The study group comprised 46 non-retarded patients and 54 mentally retarded patients. In most of the retarded patients, retardation was secondary to some other psychiatric disorder. Most of the target symptoms studied were severe enough to interfere with the treatment and education of the patients. Initial doses for both groups ranged from 0.75 to 6.0 mg/day; average initial doses were 2.0 and 1.9 mg/day for the retarded and non-retarded groups, respectively. Maximum doses for both groups ranged from 0.75 to 12.0 mg/day; average maximum doses were 3.0 and 3.1 mg/day for the retarded and non-retarded groups, respectively. The patients were treated for an average of 42 days, with the duration of treatment ranging from 2 to 82 days. Results showed that upon measurement of the therapeutic response of the total population, 95% of the non-retarded and 78% of the retarded patients showed some degree of improvement on haloperidol. If only those patients who had improved markedly or moderately were considered as improved, a statistically significant difference in response of retarded and non-retarded patients was noted; marked or moderate improvement was observed in 78% of the non-retarded and 37% of the retarded patients. The most common side effects were mild extrapyramidal reactions, especially muscular rigidity or spasm, or mild Parkinson- like reactions. These either disappeared spontaneously or were controlled with benztropine. Other side effects were depressed mood, drowsiness, nausea, skin erythema, excessive perspiration, hallucination, leg pain and listlessness.

Assessor's comment:
The MAH provided one placebo-controlled study in 10 emotionally disturbed children, one comparator study without placebo-arm and two open-label studies. Improving of behavioural symptoms (oppositional behaviour, relationship to peers, response to limit, hyperactivity, anxiety, aggressiveness, and impulsiveness were observed with haloperidol.

Across studies, haloperidol treatment was associated with the following adverse effects:
Extrapyramidal symptoms (slurred speech, increased salivation, increased muscle tonus, tremor of the hands, severe parkinsonian syndrome, ataxia), excessive sedation/drowsiness, lethargy, nausea, vomiting, flushing of the face, blurring of vision, diplopia, depression, endogenous depression (early awakening, morning retardation, self-reproachfulness, and a depressed mood), skin erythema, excessive perspiration, hallucination, leg pain and listlessness.

These data should be developed by the MAH in a global analysis of the use of haloperidol in treatment of behavioural symptoms in children and adolescents with pervasive developmental disorder or conduct disorder.

5.8 Use in delirium

The MAH presented a single retrospective chart review in this indication not listed in any of the EU SmPCs. The MAH stated that it is presented as an example of clinical experience.

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Grover S[45] (2009)	To study the clinical profile	Retro-spective	-	38 (24/14)	10.66 y (5-14 y)	0.25 to 3 mg/d	Delirium as ICD-10	

Grover S[45] (2009) performed a retrospective chart review in order to study the clinical profile of children and adolescents (≤ 14 y) diagnosed as delirium. Forty-six children and adolescents were diagnosed as delirium by the psychiatry consultation-liaison team. Data were available for 38 patients. The most common underlying pathology was infection of various types, followed by neoplasms. All subjects exhibited sleep-wake cycle disturbance and impaired orientation. Other common symptoms were impaired attention (89.5%), impaired short-term memory (84.2%), agitation (68.4%), and lability of affect (60.5%). Delusions and hallucinations were reported by only a few patients. The majority of patients (N=20, 53%) were treated with haloperidol (dose range of 0.25 to 3 mg per day). Only supportive behavioural management was used in nine (24%) patients. Other drugs used included lorazepam (N=5, 13%; dose range 0.5 to 2 mg), risperidone (N=3, 8%; dose range 0.25 to 1 mg), and thioridazine (N=1; dose 25 mg). All patients were on medications to treat their underlying medical/surgical illness. The mean duration of delirium after starting treatment was 3.89 days and 63% of the patients were reported to be free of all symptoms of delirium by 1 week. None of the patients died. The authors concluded that phenomenology of delirium is suggestive of global encephalopathic dysfunction, irrespective of etiological diagnosis. Also, the majority of patients were treated with haloperidol and other antipsychotics and showed clinically significant improvement in about 4 days.

Assessor's comment:
According to this single retrospective study with small number of children and adolescents, no recommendation can be made on the use of haloperidol in delirium.

5.9 Intravenous use in critically ill children with agitation and delirium

The MAH provided two retrospective reviews in this indication not listed in any of the EU SmPCs. The MAH stated that it is presented as an example of clinical experience.
Furthermore the intravenous administration was removed from the CCDS as of December 2009. Haloperidol solution is recommended for intramuscular use only.

First author Date	Study Objective	Design	Subjs by arm entered/ compl M/F	Mean Age
Brown RL[46] (1996)	Efficacy and safety of HAL	Retrospective review	30 (24/6)	7 y (8 months-18 y)
Ratcliff SL[47] (2004)	Efficacy and safety of HAL	Retrospective review	26 (19/6)	11.7 y

Brown RL[46] (1996) reviewed the medical record of 30 critically ill, paediatric patients with burns treated with haloperidol during the period of August 1986 to March 1992. The efficacy of haloperidol was scored on a scale of 0 to 3 (0= no effect, 1= fair, 2= good, 3= excellent) based on a retrospective review of the nursing notes. The mean age of the patients was 7.0 ± 1 years (8 months to 18 years) with 53% (16) from birth to 5 years of age. All patients had sustained significant burn injuries.
The major indication for the use of haloperidol was marked agitation and restlessness (80%), followed by delirium with marked disorientation, hallucinations, and delusions (13%) and insomnia (7%). All patients were treated with various combinations of other medications before and/or concurrent with administration of haloperidol, including opioid analgesics, benzodiazepines, barbituates, and chloral hydrate. A total of 429 doses of haloperidol were administered over this period. The mean dose of haloperidol used was 0.047 ± 0.002 mg/kg (0.009 to 0.227 mg/kg). The largest cumulative dose administered over a 24-hour period was 0.455 mg/kg. The mean number of doses given was 14 ± 4 (1 to 113). The largest number of doses given over a 24-hour period was 6. The longer period of treatment with haloperidol was 3 months.
Routes of administration included IV, enteral, and intramuscular (IM). Forty-three percent (184/429) of doses were IV, and 57% (244/429) were enteral. One patient (0.23%) received a single IM dose of haloperidol. The predominant routes of administration were IV in 60% (18), enteral in 37%, (11), and IM in 3% (1). The mean efficacy score was 2.30 ± 0.21 (good). Twenty patients (67%) had an efficacy score of 3, four patients (13%) had an efficacy score of 2, and one patient (3%) had an efficacy score of 1. Haloperidol had no beneficial effect in five of the 30 patients (17%). The enteral route was used in four of the five patients in which haloperidol had no beneficial effect. When documented (in seven patients), the interval between IV administration of haloperidol and onset of effect was within 30 minutes.
Of the 429 doses of haloperidol that were administered, adverse effects were noted on only two occasions: a brief period of decreased consciousness in a 7-year-old child, resolving spontaneously, and a brief period of hypotension in a 14-year-old adolescent, which resolved promptly with fluid administration. The authors concluded that haloperidol may be safely and effectively used in the critical care setting to treat severe agitation and delirium in the paediatric patient with burns. The IV route appears to be more effective than the enteral route. Effects may be seen sooner with the IV route because of the pharmacokinetic properties of haloperidol. The IV route should be considered when rapid, acute control of agitation is required.

Ratcliff SL[47] (2004) assessed the effectiveness and safety of the use of haloperidol by a retrospective chart review of 855 acutely ill suffering burns children treated consecutively during the period from April 1999 to May 2002. A total of 26 of these children received haloperidol and therefore were included in this study. The efficacy of haloperidol was scored on a scale of 0 to 3 (0= no effect, 1= fair, 2= good, 3= excellent).
The major indication for the use of haloperidol was marked agitation and restlessness (85%). The other indication for the use of haloperidol was agitation and restlessness in addition to delirium with marked disorientation, hallucinations, and delusions (15%). Like typical critically ill trauma and acute burn patients, these patients were treated with various combinations of pain and anxiety medications before and/or concurrent with administration of haloperidol (analgesics, anxiolytics, management of acute stress disorder, antipruritic).
A total of 308 doses of haloperidol were administered during the period of April 1999 to May 2002. The mean dose of haloperidol used was 0.057 mg/kg (0.013 to 0.278 mg/kg). The largest cumulative dose administered during a 24-hour period was 0.957 mg/kg. The mean ± SD of the number of doses given was 12 ± 30 (range, 1-153). The largest number of doses given during a 24-hour period was 12. The longest period of treatment with haloperidol was 22 days. The six patients with adverse side effects received more total haloperidol during a longer period of time than those who did not have adverse effects (total HAL doses in 24 hours: patients with no AE = 3.7±5.6 vs patients with AE=9.7±4.6; total doses of IV HAL: no AE=5±5, AE=14±9; total doses of enteral HAL: no AE=138±0, AE=3±3). These differences occurred despite the fact that those with adverse reactions had slightly smaller burns. Routes of administration included intravenous and enteral. Fifty-three percent (164/308) of doses were intravenous, and 47% (144/308) were enteral. Twenty-three patients received haloperidol by intravenous administration, one patient by enteral administration, and two received it by a combination of the two. The mean effectiveness score of haloperidol was 1.73, with a median effectiveness between 1 and 2 (fair to good effect).
Of the 26 patients included in the study a total of 6 patients (23%) had 7 adverse reactions to the medication (5 dystonic reactions, 2 hyperpyrexias). The authors concluded that haloperidol should be reserved only for acute situations. Patients must be constantly monitored so that maintenance therapy is tailored to the individual patient and that extrapyramidal system symptoms can be managed appropriately.

Assessor's comment:
The MAH provided two retrospective studies on the use of haloperidol IV in critically ill children with agitation and delirium. However, the IV administration was removed from the CCDS as of December 2009.

5.10 Use in children Review

First author Date	Study Objective	Design
Serrano AC[48] (1981)	Efficacy and safety of HAL	Retrospective review

Serrano[48] (1981) described in a review the use of haloperidol in children. His findings were:

- In children with psychotic symptoms (psychoses, mental retardation, autism), haloperidol may help to relieve symptoms as hyperactivity, aggressiveness, selfmutilation, rage, explosive outbursts, withdrawal, and stereotypy in some disturbed children so that they become more manageable, educable, and amenable to such other therapies as individual, family and group psychotherapy, behaviour modification, and remedial education.

- In children with non-psychotic symptoms (hyperkinetic symptom or minimal brain dysfunction), haloperidol may be useful to bring acute, severe episodes under control, or for management of difficult cases when stimulant drugs, such as methylphenidate and amphetamine, have been tried without success. It is usually reserved for short-term use. The author stated that haloperidol minimally affects alertness and cognition and does not oversedate the young patient except for some initial dose-related drowsiness.
- In children with Tourette's syndrome, haloperidol has been found to be quite effective in reducing or even eliminating the manifestations of this disorder, which is often resistant to other forms of treatment. Symptoms usually regress within 24 to 48 hours after therapy begins, and often disappear completely with adjustment of haloperidol dosage.
- A suggested starting dose for children with psychotic symptoms or Tourette's is 0.025 to 0.05 mg/kg body weight per day. The daily amount is usually divided and given as two or three equal doses. The starting dose is gradually increased (e.g., over a period of two or three weeks), until target symptoms are controlled. Dosage is then adjusted to the lowest level that will maintain this control. Maintenance amounts have ranged from 0.04 to 0.07 mg/kg/day. Short-term therapy of four to six weeks may suffice for an acute psychotic episode, for example, while children with chronic conditions or with intrinsic disorders (e.g., organic brain syndrome) may need therapy for long periods. When children require long-term therapy, it may be advisable to try lowering the dosage periodically in order to keep the maintenance dose as low as possible. Haloperidol therapy should be stopped when the drug is no longer needed. Several investigators have suggested interrupting long-term therapy for a week or two after every three or four months of treatment. Such "drug holidays" allow an assessment of the child's clinical status.
- The most commonly seen side effects are an initial drowsiness and extrapyramidal symptoms (EPS). The drowsiness appears to be dose-related, and when it occurs it usually disappears within a few days with continued administration of the drug. If drowsiness does not disappear, it usually improves with downward dosage adjustment. The EPS tend to occur early in the course of therapy, and with larger initial doses. The procedure of starting with a very low dose and increasing it gradually should help to reduce their incidence and severity. EPS can often be relieved by a reduction in dosage; if this is unsuccessful, they can be treated with antiparkinsonian agents. Slight weight gain is often seen in children receiving haloperidol. Long-term neuroleptic therapy can cause tardive dyskinesia.

Assessor's comment:
The retrospective review of the use of haloperidol in children is dated from 1981. The author mentioned the most described uses of haloperidol from literature, which were related to the psychomotor anti-agitation property of haloperidol.
According to the authors, the most commonly seen side effects are an initial drowsiness, extrapyramidal symptoms and weight gain.

6 Safety

The MAH provided 2 safety publications.

First author Date	Study Objective	Design	Duration	Subjs by arm entered/ compl M/F	Mean Age	Treatments	Diagnosis Incl. criteria	Outcomes/ endpoints
Armenteros[49] (1995)	Relationship between pre- and perinatal complications and TD/WD	Prospective		118 (95/23)	4.98 y (2.3-8.2 y)		Autism as DSM-III-R criteria	ROS AIMS
Siva S.[50] (1993)	Effects of HAL on weight	Prospective	6 months	30 (25/5)	5.72 ±1.46 y (3.08-8.42 y)	1.26 ± 0.84 mg/d (0.25-3.50 mg/d)	Autism as DSM-III criteria	

TD: tardive dyskinesia, WD: withdrawal dyskinesia, ROS: Rochester Research Obstetrical scale, AIMS: abnormal involuntary movement scale

Armenteros[49] (1995) examined whether an association exists between pre- and perinatal complications and the subsequent development of haloperidol related tardive and withdrawal dyskinesia (TD/WD) in children with autism.

The sample consists of 118 subjects, 95 males and 23 females, ages 2.3 to 8.2 years (mean=4.98), who participated in an ongoing long-term prospective study of the efficacy and safety of haloperidol. All children met DSM-III criteria for infantile autism or DSM-III-R criteria for autistic disorder with onset in infancy. The level of intellectual functioning of the children ranged from profoundly retarded to normal. TD is defined as abnormal movements developing while the subject is receiving haloperidol; WD is defined as abnormal movements emerging after the discontinuation of haloperidol. Pre- and perinatal complications were rated on the ROS (Rochester Research Obstetrical scale) which includes Prenatal, Delivery, and Infant Scales in addition to a Total Score. The ROS ratings of the children who developed TD/WD (n=40) were compared to the ROS ratings of those who remained free of TD/WD (n=78).

In the sample of 118 children, 40 developed TD/WD (33.9%) and 78 remained free of TD/WD (66.1%). The cumulative exposure to haloperidol prior to TD/WD ranged from 56 days to 5 years. In 5 children the onset of dyskineias occurred during treatment with haloperidol and were diagnosed as TD. In the remaining 35 children, the dyskinesias occurred after haloperidol withdrawal and were diagnosed as WD. The majority of children (n=19 or 47.5%) had WD, emerging after the first 6 months of treatment with haloperidol, during the 4-week drug withdrawal period. Of the 40 children with TD/WD, 32 (80%) had an onset during the first 21 months of the study; only 8 (20%) developed TD/WD subsequently.

ROS mean total score was 3.87 for subjects who developed TD/WD and was statistically significantly higher than the mean total ROS score (2.87) for those who did not develop TD/WD. There were no significant differences in the mean total ROS scores between the children with TD and those with WD. The mean ROS Delivery Scale score (2.45) was also statistically significantly higher for subjects who developed TD/WD than for the subjects who did not develop TD/ WD. The authors concluded that the pre- and perinatal complications as measured by the ROS appear to be related to the development of TD/WD in the sample of children with autistic disorder.

Siva S.[50] (1993) assessed the long-term effect of haloperidol and withdrawal on weight in 30 children (5.72 y) diagnosed with autistic disorder in a prospective long-term study. Haloperidol was administrated for 6 months followed by a 4-week drug withdrawal period during which placebo was administrated. The weights from the last day of the 6-month haloperidol treatment period were compared to weights taken weekly at the end of each of the 4 weeks of the placebo periods. The data were analyzed using a one-way analysis of variance (ANOVA) with repeated measures. For 22 subjects in this study the 6-month haloperidol period represented their first 6-

month cycle of haloperidol administration; in 4 cases it was the second 6-month cycle. Of the remaining 4 patients, one patient each was in the third, fourth, fifth, and seventh 6-month cycle of haloperidol administration.
Daily haloperidol doses for the 30 subjects ranged from 0.25 to 3.50 mg (mean = 1.26 ± 0.84) or 0.012 to 0.208 mg/kg (mean = 0.056 ± 0.046) at the end of the 6-month treatment period. From the end of the 6-month haloperidol period to the end of the first week of haloperidol withdrawal, 7 of the 30 subjects lost weight ranging from 0.11 to 0.45 kg (mean = 0.27 ± 0.14), 13 children gained from 0.11 to 0.68 kg (mean = 0.32 ± 0.11), 9 subjects did not show any change in weight, and mean weights increased. During each of the next 3 weeks of placebo treatment, mean weights decreased.
There was no significant difference between the mean weights obtained on the last day of haloperidol administration (24.799 +/- 9.741 kg) compared to the mean weights at the end of the fourth week of the placebo period (24.644 +/- 9.833 kg). Weights increased during the first week of drug discontinuation (24.879 +/- 9.855 kg), but decreased during each following week of drug withdrawal. Weight was measured monthly during the 6-month haloperidol treatment period for 8 of the 30 subjects. In this subsample, weight gain was greater during the 1-month period, lasting from the end of the 4-week drug withdrawal to the end of the first month after resuming haloperidol treatment, than weight gain prior to drug withdrawal, between the fifth and sixth month of haloperidol treatment.

Assessor's comment:
The 2 publications on haloperidol safety provided by the MAH are not sufficient to describe the overall safety profile of haloperidol in children and adolescents.

7 Discussion on clinical aspects

Clinical data provided by the MAH are issued from literature: 49 publications dated from 1967 to 2009 with only 8 dated after 2000. The MAH did not provide a global overview and analysis of these data.

In the literature review, the higher number of publications was in schizophrenia, in Tourette's Disorder, and in autistic disorder, the most commonly indications approved in EU.
According to the literature data provided by the MAH, no recommendation can be made on the use of haloperidol in schizophrenia and in Tourette's Disorder, because of insufficient validated efficacy data, lack of long-term efficacy studies, and the poor safety profile of haloperidol in children and adolescents.
No recommendation can be made on the other specific use of haloperidol reviewed by the MAH (aggressiveness, ADHD, anxiety-tension states, emotionally disturbed children with heterogeneous diagnoses, delirium and IV use in critically ill children with agitation and delirium) because of the small publications provided, the poor study design, and the small number of patients. No data in use of haloperidol in post-operative nausea and vomiting were provided.

However, sufficient efficacy data on behavioural symptoms seem to be available but are dispatched between several publications (autistic disorder and pervasive developmental disorders, aggressiveness, emotionally disturbed children).

In Autistic disorder, most of placebo-controlled studies were in cross-over. These publications are old and clinical data provided are incomplete. However, across the 7 placebo-controlled, 2 comparator-controlled and 4 open-label studies, significant decreases in behavioural symptoms as withdrawal, stereotypy, hyperactivity, agressiveness were frequently described. Especially, in

one recent double-blind, randomised, 8-week, no placebo-arm study (Miral S.[32], 2008) which compared risperidone and haloperidol in the treatment of autistic disorder.

These data should be reconsidered with data from publications in children[48] with conduct disorder[37] or heterogeneous diagnosis[41,42,43,44]. Haloperidol seems to have an interest as symptomatic treatment in hyperactivity, impulsivity, aggressiveness. Short-term symptomatic treatment should be initiated only when psychosocial and educational interventions are not sufficient.

In most publications, adverse events were described. Undesirable effects practically observed in all studies were Extrapyramidal symptoms (acute dystonia, akathisia, akinesia, and increased salivation) and excessive sedation/drowsiness which was described as dose-related. Frequency of Extrapyramidal symptoms may be underestimated because of anticholinergic treatment frequently associated with haloperidol treatment.
The others adverse events frequently described were weight gain, depression, anxiety and nausea.
With a smaller frequency, QTc prolongation, serum prolactin level increase, irritability, lethargy, listlessness, lassitude, orthostatic hypotension, light-headedness, poor appetite/anorexia, vomiting, flushing of the face/skin erythema, blurring of vision, diplopia, excessive perspiration, hallucination, leg pain, constipation, enuresis nocturna, blunted affect, difficulty sleeping, upper respiratory tract infection, diarrhoea, and a case of neuroleptic malignant syndrome were described.
Hyperprolactinemia was described in one clinical study and in a pharmacodynamic study (Wudarsky[2], 1999).

Safety profile of haloperidol in children and adolescents appears poor with a significant frequency of EPS and sedation. Other adverse events as depression, weight gain, irritability, lethargy, QT prolongation, neuroleptic malignant syndrome, prolactin level increase are major concerns in children and adolescents.

As haloperidol is marketed in EU since 1959 and used in paediatric indications in the majority of EU member states, postmarketing data are available and evaluated thought PSURs, which were not provided by the MAH as part of this worksharing procedure.
The MAH should provide the line listing from 2000 of adverse effects occurring in patients less than 18 years by SOC, with 2 listing according to serious or non-serious CIOMS forms.

8 Preliminary rapporteur's overall conclusion and recommendation

On the CCDS of the MAH, haloperidol can be used as "a psychomotor anti-agitation agent in disorders of behaviour and character in children at the dose of 0.1 mg/3 kg weight TID orally; may be adjusted if needed".

From the Rapporteur's point of view, the CCDS wording and information should be updated:
Atypical antipsychotic are preferentially prescribed as first-line in children and adolescents.
Haloperidol may have an interest as an alternative of atypical antipsychotic in persistent aggression in children.
Haloperidol may be a symptomatic short-term (maximum 4-week) treatment in case of persistent hyperactivity and aggression when psychosocial and educational interventions are not sufficient, in children 3 years and older with conduct disorder or pervasive developmental disorders.

In the other indications (psychoses including schizophrenia, Gilles de la Tourette's disorder), based on submitted publications, no recommendation of use could be made because of lack of sufficient data on efficacy and the safety profile of haloperidol in children and adolescents.

The MAH proposes to change the dose as follow: "treatment should start with 0.025-0.033 mg/kg weight orally three times a day and should be adjusted as necessary. The maximum recommended daily dosage is 0.28 mg/kg/d, based on dosages studies in clinical trials of haloperidol in children".
According to the provided data and the indication, the starting dose should be 0.25-0.5 mg/d and then, increased slowly at regular interval. The maximum daily dose should not exceed 4 mg.
The MAH dosage proposal is equivalent to the dosage usually used in clinical studies and then, could be accepted with the supplementary mention that dose increase should be progressive.

Warning in paediatric population on the risk of the use of haloperidol in children (i.e. excessive sedation, extrapyramidal symptoms, hyperprolactinemia and its consequences, weight gain) should be clearly stated into the section 4.4. of the CDDS. The MAH should also detailed adverse effects observed in paediatric population into the section 4.8.

- **Overall conclusion**

Based on the data submitted, haloperidol could be used in children 3 years and older as symptomatic short-term (maximum 4-week) treatment in case of persistent hyperactivity and aggression when psychosocial and educational interventions are not sufficient, in children with conduct disorder or pervasive developmental disorders.
However, global literature data analysis from the MAH is lacking at the present time to make a final recommendation.

- **Recommendation**

The MAH should provide a global analysis on the use of haloperidol as psychomotor anti-agitation agent in children with conduct disorder or pervasive developmental disorders, clarifications, and CCDS updates (sections 4.2, 4.4 and 4.8). (see section IV "Request for supplementary information".)

9 Preliminary request for supplementary information

The MAH should provide a global analysis on the use of haloperidol as psychomotor anti-agitation agent in children with conduct disorder or pervasive developmental disorders according to the submitted data and discuss:

- The aimed symptoms
- The definition of the paediatric population (diagnosis and age range)
- The dose schedule
- The dose by weight
- The duration of treatment
- The precaution of use
- The undesirable effects

The MAH should provide CCDS updates (sections 4.2, 4.4 and 4.8), with a warning in paediatric population on the risk of EPS, excessive sedation, hyperprolactinemia and weight gain.

The MAH should provide the line listing from 2000 of adverse effects occurring in patients less than 18 years by SOC, with 2 listing according to serious or non-serious CIOMS forms.
The MAH should precise if frequency and nature of EPS in children and adolescents differs from those of adults.

10 Comments received

Comments received from Member States were as follows:

1. The diagnose Conduct disorder is not compatible with the very low age of 3 but from prepubertal age (10 years of age is suggested) only.
2. Data is lacking with regard to efficacy as well as safety to support the use of haloperidol at such low ages as 3 years of age.
3. MAH should provide data to support a positive R/B balance with stratified data for ages below 18.
4. Atypical antipsychotics are preferably used instead of haloperidol in pervasive developmental disorders as supported by a clinical study (Miral S, 2008) with regard to overall R/B evaluation.

A revised overall conclusion is proposed:
Haloperidol could be used in children 10 years and older as symptomatic short-term (maximum 4-week) treatment in case of persistent hyperactivity and aggression when psychosocial and educational interventions are not sufficient, in children with conduct disorder or pervasive developmental disorders.
However, global literature data analysis from the MAH is lacking at the present time to make a final recommendation.
The recommendation by the Rapporteur that "The MAH should provide a global analysis on the use of haloperidol as psychomotor anti-agitation agent in children with conduct disorder or pervasive developmental disorders, clarifications, and CCDS updates (sections 4.2, 4.4 and 4.8) is most supported.

- What is the likely long-term benefit of this short intervention in children with conduct disorders or pervasive developmental disorders?
- To what extent is the benefit if it exists likely to outweigh potential adverse events e.g. sedation, tardive dyskinesia, weight gain etc?
- If this indication is agreed should prescribing be limited to Child psychiatrists who specialise in treating these disorders?
- Conduct disorders often co-exist with ADHD where first line treatment is unlikely to be an anti-pyschotic

We recognise that the evidence base on pharmacotherapy for aggression in this group of children and young people is limited. A guideline from the US National Guideline Clearing House "Best evidence statement (BESt). Pharmacological treatment of aggression in children with attention deficit hyperactivity disorder (ADHD)" states that "Atypical antipsychotics are preferred over typical antipsychotics for the treatment of aggression because they have a lower risk for tardive dyskinesia, neuroleptic malignant syndrome, cognitive impairment, and extrapyramidal symptoms (Pappadopulos et al., 2003 [5a]). http://www.guideline.gov/content.aspx?id=15628

- Efficacy data is insufficient, mostly consisting of small old crossover studies, the description of which in the submitted publications is not sufficiently detailed.
- The submitted evidence suggests that risperidone has superior efficacy compared to haloperidol.

- Safety profile of haloperidol in children and adolescents is poor and especially, for short term use, there are concerns about effects on EPS. Also long-term safety data is lacking (i.e. even (repetitive) short-term treatment might have long-term safety implications i.e. on (sexual) maturation, cognition, endocrine function, changes in prolactin levels and other aspects of development).

Notwithstanding this negative position, as a general comment:

- the proposed indication suggests that children from the age of 3 can be treated, and that targeted symptoms are not only aggression but also hyperactivity. For such a "heavy" medication this is unacceptable since age 3 is considered too young (even risperidon for which there is much more evidence is indicated from the age of 5) and hyperactivity is not an acceptable treatment target.
- the studies do not lend any support for a second line indication, i.e. patients recruited were not shown to be unresponsive to psychosocial and educational interventions.

Regarding the dose recommendation: Given the fact that granting an indication for children is not supported, providing a dose recommendation for children and adolescents since it will promote off-label use.

<u>The following text is therefore proposed for section 4.2</u>:
The safety and efficacy of haloperidol in children has not been established. Currently available data are described in section 4.4 and 4.8 but no recommendation on a posology can be made

Note that the acceptability of the last sentence and inclusion of information on children in sections 4.4 and 4.8 will depend on the proposals to be provided by the company.

Of further note: notwithstanding our negative opinion it is noted that the proposed dose is considered much too high when comparing it to available treatment protocols where off-label use of haloperidol is prescribed (normally 0.01 mg/kg/day).

V. SCIENTIFIC DISCUSSION ON MAH RESPONSES

V.1 Efficacy

The MAH's response document was composed by an overview evaluating the efficacy of haloperidol as a psychomotor anti-agitation agent in treating behavioural symptoms (such as persistent hyperactivity and aggression) that were present in children diagnosed with autistic disorder and pervasive developmental disorders, aggressiveness, and in emotionally disturbed children with heterogeneous diagnoses.

According to the current CCDS, haloperidol is indicated as a psychomotor anti-agitation agent for "the treatment of disorders of behaviour and character in children". No other indications for this specific age group are listed in the CCDS. The recommended dose in children is "0.1 mg/3 kg body weight TID orally; may be adjusted if needed".

On the 20 studies reported in the Clinical Overview dated 20 July 2010 provided to Afssaps, 11 were selected and described by the MAH in the table 1 (Terms in **bold-red** indicate symptoms which improved with haloperidol treatment. Terms in **bold-black** indicate symptoms which did not improve with haloperidol).

The MAH proposed the following wording for the SmPCs:

4.1 Therapeutic indications
Delete "*disorders of behaviour and character in children*" under the sub-heading "*As a neuroleptic agent in*" and replace it with a separate paragraph under this sub-heading.
Paediatric population:
Treatment of behavioural symptoms of psychomotor agitation (such as persistent hyperactivity and aggression) in children over the age of 5 years diagnosed with autistic disorder and pervasive developmental disorders, aggressiveness and emotional disturbance.

4.2 Posology and method administration
Delete "*In children: 0.1 mg/3 kg body weight TID orally; may be adjusted if needed*" and replace this with a separate paragraph.

Paediatric population
In children 5 years and over, treatment should start with 0.025-0.033 mg/kg weight orally three times a day and should be adjusted as necessary. The maximum recommended daily dosage is 0.28 mg/kg/d, based on dosages studied in clinical trials of haloperidol in children.

4.4 Special warnings and precautions for use
Paediatric population
Sedation may occur more commonly in children.

No wording was proposed for the sections 4.8 and 5.1.

Table 1. List of studies evaluating the efficacy of Haldol as a psychomotor anti-agitation agent in treating behavioural symptoms

First author (year)	Dosage	Comparator	Report type	No. of patients haloperidol/ total (age range)	Patient diagnosis	Efficacy results	Safety results
Campbell[1] (1978)	(Range: 0.5-4mg/d). Mean optimal dose; 1.65 mg/d Increments were done twice a week at regular intervals over a period of 3 weeks (steps were: 0.5, 1.0, 1.5, 2.0, 3.0, and 4.0 mg/d). Optimal dosage was determined on an individual basis for each child.	Placebo	Double-blind placebo controlled	20/40 (2.6-7y)	Autism	For children above 4.5 years, haloperidol was significantly superior to placebo in reducing the severity of **withdrawal and stereotypy**. **Hyperactivity, hypoactivity, psychotic speech, abnormal object relations, or irritability (angry affect)** were not significantly affected by haloperidol. For children below 4.5 years old, there was no significant improvement in any of the symptoms. Though the results of the study did not indicate a significant effect of haloperidol on hyperactivity, 9 children, discharged from the hospital without drug therapy, were brought back by their parents who requested haloperidol treatment. The children exhibited hyperactivity and/or temper tantrums at home, and in special educational programs	The most common untoward effect was excessive sedation, which was dose dependent. The relative frequency of sedation (number of children sedated/total number of children experiencing that dose was 5, 21, 7, 8, 11 and 56% at 0.5, 1.0, 1.5, 2.0, 3.0 and 4.0 mg/day, respectively). Older children (>4.5y) tolerated higher optimum doses (0.15 mg/kg/day) than the younger children (0.07 mg/kg/day). Overall, the side effects on haloperidol were transient, seen primarily during the dosage regulation phase, and were controlled by dose reduction. There were no significant differences in body weight between the haloperidol and placebo groups at any time during the study.
Anderson[2] (1984)	(Range: 0.5-4 mg/d). Optimal doses ranged from 0.5 to 3.0 mg/d (mean, 1.1) and 0.019 to 0.217 mg/kg/d (mean, 0.05).	Placebo	Double-blind placebo controlled	40/ (2.33-6.92y)	Autism	Children receiving haloperidol showed significant decreases in symptoms of **withdrawal, stereotypy, hyperactivity, abnormal object relationships, fidgetiness, negativism, irritability (angry affect), and lability of affect (emotional lability).**	Untoward effects were noted only on doses above the optimum or during the dosage titration period (0.5 to 4.0 mg/day). The most frequent untoward effects above optimal doses or during the regulation period were excessive sedation and increased irritability. Acute dystonic reactions were observed in 11 children during dosage titration.
Anderson[3] (1989)	Range: 0.25-4mg/d (0.016-0.184 mg/kg/d)	Placebo	Double-blind placebo controlled	45/ (2-7.5y)	Autism	Haloperidol decreased **hyperactivity, temper tantrums, withdrawal and stereotypy**. The children were calmed without being sedated.	By careful adjustment of the dosage for each individual child, none of the 45 patients had untoward drug effects at therapeutic doses.
Cohen[4] (1980)	Initial: starting dose 0.5 mg/d up to 4 mg/d. Optimal doses ranged between 1.65-1.90 mg/d in completing patients	Placebo	Double-blind placebo controlled, crossover	10/ 10 (2.1-7y)	Autism	Haloperidol had no effect, at optimum doses, on the percent occurrence of **walking, affect, social behaviour, lack of speech, hyperactivity, or hypoactivity**. Haloperidol was found to be effective in reducing relatively high percentages of **stereotypy** and increasing relatively low percentages of **attending to the rater**. Age, in addition, was a relevant variable. In general, the older children responded better than the younger, in agreement with data of a previous study of the same authors [1].	Excessive sedation was apparent in 8 out of 10 of the children on doses of haloperidol above optimal, ranging from 1.0 mg/day to 4.0 mg/day. Acute dystonic reaction occurred twice in 1 child, first, at a dose of 1.0 mg bid and then again when the dose was lowered to 0.5 mg bid. All laboratory tests remained within normal limits.
Remington[5] (2001)	Mean: 1.3 mg/d; Range: 1-1.5 mg. Dose increments were 0.25 mg at bedtime for 2 days, 0.25 mg twice a day for 2 days, 0.25 mg three times a day for 2 days, and 0.5 mg twice a day; thereafter, haloperidol doses were increased in 0.5 mg increments every 3 or 4 days	Placebo Clomipramine	Double-blind placebo controlled, crossover	-/36 (10-36y)	Autism	Haloperidol proved superior to baseline on a global measure of autistic symptom severity, as well as specific measures for **irritability and hyperactivity**. No differences were detected for stereotypic behaviour, **lethargy, or inappropriate speech** for the intent to treat population. However, when the analysis was repeated for completers, **stereotypy** was also significantly improved versus baseline. The placebo group was not superior to baseline on any measures	In the haloperidol trials, 10 of 33 subjects were prematurely discontinued, with identified side effects accounting for 7 of these: fatigue or lethargy, N = 5; dystonia] N = 1; and depression, N = 1.

Naruse[6] (1982)	Range: 0.75-6.75 mg/d	Placebo Pimozide	Double-blind placebo controlled, crossover	87 (3-16y)	Different diagnoses (Autistic disturbance, psychosis, neurosis, hyperkinetic syndrome and mental retardation)	Haloperidol was superior to placebo in the two symptom clusters "mental disorder" and "abnormal symptoms". The individual symptoms (imcluded in the Rating Scale for Abnormal Behavior in Children) that improved significantly with haloperidol were: **hyperkinesia; hypokinesia, happiness/pleasure, anxiety (angor), autistic tendency, familiarity, aggressiveness, self-centeredness, breaking furniture, and echosymptom (e.g., echolalia, echopraxia).** The following symptoms did not improve significantly with haloperidol treatment: **sadness, fear, lability of mood, expression, "stickiness", stubbornness, diversibility/distractability, hasty act, positiveness/spontaneity, passivity, interest, shyness, refusal, dependency on others, non-self-help, flaunting, interference/management, habit/tics, self-mutilation, stealing, injury and violence to others, speech disorders, sexual disorders, anxiety, hypochondria, phobia, obsession, stereotypy, negativism, "disturbance of self", hallucination/delusion, pathological fantasy, disturbance of thought.**	Both pimozide and haloperidol produced more sleepiness than the placebo ($p<0.01$). There was no significant difference between pimozide or haloperidol and placebo in frequency of other side-effects.
Joshi[7] (1988)	Range:1.3 to.7 mg/d; mean:0.04 ±0.01 mg/kg/d	Fluphenazine	Open study	12 (7-11y)	Pervasive developmental disorder	While receiving an average dose of 0.04 mg/kg per day of haloperidol or fluphenazine hydrochloride, the patients exhibited significant reductions in hyperactivity and aggressive symptoms and significant improvement in peer relations. This dose of neuroleptic was associated with minimal side effects. Clinical observations and rating scale assessments indicated remarkable improvement in **peer interactions, reduction in autistic-like behaviours, improved reality testing, and decrements in impulsivity and hyperactivity** with low-dose neuroleptic treatment. **Preoccupation with fantasies and morbid interests as well as resistance to change** appeared to be considerably reduced, as supported by follow-up testing in five of the 12 patients.	Untoward effects were remarkably infrequent. Drowsiness occurred initially in some children, but it was transient and did not interfere with their later cognitive performance. Two children receiving haloperidol developed some rigidity and cogwheeling that responded to oral diphenhydramine during the first few days of treatment; the extrapyramidal symptoms did not recur when the diphenhydramine was discontinued.
Campbell[8] (1984)	Start dose 1mg/d, then gradual increments; Optimal dose was 0.04 to 0.21 mg/kg/d (or 1-6 mg/d) (mean, 0.096 mg/kg/d). The maximum dosage given during the regulation period ranged from 1.5 to 12.0 mg/d	Lithium/ Placebo	Double-blind, placebo-controlled	20/61 (5.2-12.9y)	Conduct disorder, undersocialized, aggressive (DSM III)	Both haloperidol and lithium were superior to placebo in ameliorating behavioural symptoms. The **hyperactivity, aggression, and hostility clusters** were highly significantly improved with haloperidol.	The most common side effects with haloperidol were excessive sedation, acute dystonic reaction and drooling (of the 16 children who were sedated, four continued to be so with optimal dose). The average number of untoward effects per child during optimal dose were not significantly different between the haloperidol/placebo. However, the untoward effects of haloperidol during optimal dose seemed to interfere with the child's daily functioning more than those seen with placebo. The number of untoward effects with optimal dosage decreased with age of the subject receiving haloperidol.

Lucas[9] (1969)	0.5 mg starting dose, raised by 0.5 mg/d until effectiveness or side effects; no mg/kg/d provided	Placebo	Double-blind, placebo-controlled, cross-over	15/ 15 (8.5-15.5; mean: 12.4 y)	Psychoneurosis (4), brain damage (3), schizophrenia (3), personality disorder (3), psychopathy (2)	For three of the behavioral categories (**oppositional behaviour, relationship to peers, and response to limit setting**) behaviour was significantly improved during drug administration as compared to placebo. No significant improvement was observed for behavioural ratings on **hyperactivity, anxiety and tension, aggressiveness, impulsivity, relationship to adults, need for limit setting or participation in program**.	Drowsiness and lethargy were commonly encountered at effective dosing levels, and in 8 of the 15 patients they were prominent features. Slurred speech and increased salivation were noted in 4 patients. Four experienced nausea, and 3 increased muscle tonus. One patient had a tremor of the hands. Some developed a severe Parkinsonian syndrome, but 3 required treatment with benztropine. In 2 patients, flushing of the face was noted, and blurring of vision and diplopia occurred in one. Five patients experienced no side effects; three of these were among the patients who did not improve with haloperidol, raising the question of whether they were receiving sufficiently large doses. Laboratory studies did not change appreciably during the study
Ucer[10] (1969)	0.75 mg starting dose, raised by 25 mg every 3 days until daily dose of 3.75 mg, after week on maximum lowered to maintenance dose; mean maintenance dose: 2.25 mg	Thioridazine	Randomised, double-blind, active controlled	26/ 50 (7-12y)	Chronic brain syndrome with behavioural disorder, psychoneurosis, schizophrenia, personality disturbance	Haloperidol produced significant global improvement and significantly reduced **hyperactivity, anxiety, aggressiveness, and impulsiveness** after 8 weeks of medication. Neither drug significantly reduced **withdrawal or hostility**.	No serious side effects or pathologic changes were encountered during the study. Most of the side effects were usually mild and extrapyramidal symptoms were easily controlled with trihexyphenidyl hydrochloride. Fifteen of the twenty six haloperidol patients experienced thirty-one side effects and four of the twenty-four thioridazine patients experienced six side effects. Four haloperidol patients and one thioridazine patient were dropped from the study due to side effects. There was one case of vomiting and ataxia in the thioridazine group and three cases of ataxia and one case of vomiting in the haloperidol group. One case in the haloperidol group developed severe extrapyramidal symptoms but he was found to be suffering from Sydenham's chorea. In the thioridazine group there was significant weight gain while in the haloperidol group the weight gain was not significant. There were no significant changes in blood pressure, pulse rate or laboratory values in the two groups
Le Vann[11] (1969)	Initial doses: 0.75 to 6.0 mg/d; Average initial doses: 2.0 and 1.9 mg/d for the retarded and non-retarded groups; Maximum doses: 0.75 to 2.0 mg/d; Average maximum doses were 3.0 and 3.1 mg/d for the retarded and non-retarded groups	-	Open study	100/ 100 (6-22y)	Childhood schizophrenia, schizo-affective, juvenile autism, behavioural disorder	Haloperidol was effective in reducing **hyperactivity** (75 patients), **"assaultiveness"** (43 patients) and **self-injury** (31 patients), **excitability** (24 patients), **insomnia** (19 patients), and **poor appetite** (15 patients).	The most common side effects were mild extrapyramidal reactions, especially muscular rigidity, spasm, or mild Parkinson- like reactions. These either disappeared spontaneously or were controlled with benztropine. Of the 12 patients dropped from the study, four were dropped because of side effects. One of these developed severe leg pain and an oculogyric crisis; another had an extrapyramidal reaction and depression, and the other two had extrapyramidal reactions. Within 48 hours after stopping medication, the side effects in these four patients disappeared without treatment. Seven others were dropped due to unsatisfactory improvement, and another was dropped because of refusal to take medication.

These 11 studies were detailed by the Rapporteur on the Preliminary Assessment Report.
On the 11 studies, 6 were only performed in children with autism (Campbell 1978, Anderson 1984, Anderson 1989, Cohen 1980, Remington 2001) or pervasive developmental disorder (PDD) (Joshi 1988) and 2 additional studies included children with autism (Narus 1982, Le Vann 1969). One study included patients with conduct disorder (Campbell 1984). The other patient diagnoses were psychosis/neurosis/psychoneurosis, hyperkinetic syndrome, mental retardation, undersocialized, aggressive, brain damage, schizophrenia, personality disorder/disturbance, psychopathy, chronic brain syndrome with behavioural disorder, schizo-affective.

The majority of these studies were double-blind, randomised, versus placebo, (except Joshi 1988, Le Vann 1969) and crossover (Anderson 1984, Anderson 1989, Cohen 1980, Remington 2001, Naruse 1982, Lucas 1969). Diagnostics were mainly performed according to DSM-III or -IV (Anderson 1984 and 1989, Cohen 1980, Remington 2001, Naruse 1982, Joshi 1988) and efficacy scales used were validated (CPRS: Children's psychiatric rating scale, CBI: children behaviour inventory, CGI: clinical global impression, CARS: children autism rating scale, ABC: aberrant behaviour checklist, BRS: behavioural rating scale, TSRS: timed stereotypies rating scale, AS: abridged simpson, QBC: Questionnaire on Behavior in Children, RSABC: Rating Scale for Abnormal Behavior in Children, TPDDRS: Turgay DSM-IV pervasive developmental disorder rating scale).

Results show statistically significant improvement of scores between baseline and end of treatment on the following scales:

- Campbell (1978): on CPRS for withdrawal and stereotypy. Moreover, the combination behavioural and haloperidol treatment improved most in a language acquisition task.
- Anderson (1984): on CPRS for withdrawal, stereotypy, hyperactivity, abnormal object relationships, fidgetiness, negativism, angry affect, and lability affect, and on CGI for severity illness.
- Anderson (1989): on CPRS for withdrawal, stereotypy, hyperactivity, and on CGI for severity illness, improvement, and efficacy.
- Remington (2001): on CARS, on ABC for irritability, hyperactivity.
- Naruse (1982): on RSABC for abnormal behaviour motility (hyperkinesia with moving about, hypokinesia with moving about), affection (happiness, pleasure), human relation (autistic tendency, familiarity, aggressiveness, self-centeredness), breaking furniture, and mental disorder (echosymptom)
- Campbell (1984): on CPRS for hyperactivity, hostility and aggression, on CGI for severity of illness, global improvement and efficacy index.
- Lucas (1969): on oppositional behaviour, relationship to peers, and response to limit setting.
- Ucer (1969): on hyperactivity, anxiety, aggressiveness, hostility, withdrawal and impulsivity.

In the preliminary assessment report, the study of Miral (2008) was presented. This 12-week, randomised, double-blind study compared the efficacy and safety of risperidone and haloperidol in 28 children and adolescent with autistic disorder. In this study, risperidone appears more efficacious and safe than haloperidol. However, both risperidone and haloperidol demonstrated statistically significant improvement in several behavioural symptoms on RF-RLRS (sensory-motor and social, affect, and sensory), ABC, and Turgay DSM-IV PDD rating scale.

Overall results should be interpreted with caution because they are contradictory across studies. Indeed, same symptoms (hyperactivity, irritability, social behaviour, inappropriate speech, self-mutilation, injury, violence to other, stereotypy, aggressiveness, withdrawal, …) can be improved or not by haloperidol (please see Table above).

Dose:
Two of the reviewed studies provided information regarding the effect of age on the efficacy of haloperidol (Campbell et al. and Cohen et al.). The MAH stated that a global assessment on the effect of age on the efficacy of haloperidol could not be performed with the available data.
All the studies performed in patients with a diagnosis of autism used similar dose ranges (0.5-4 mg/day), with mean optimal dose ranging between 1.1 and 1.9 mg/day. The maximum and mean doses used for patients with “conduct disorder-undersocialized-aggressive (DSM III)” were higher (12 mg/day and 2.95 mg/day, respectively).
Starting doses in general ranged between 0.25-0.5 mg/day. Weight-adjusted dose was only provided in some studies and ranged between 0.02 and 0.05 mg/kg/day for children with autism or pervasive developmental disorder. For children with "conduct disorder-undersocialized-aggressive (DSM III)”, the mean optimal dose was higher (0.096 mg/kg/day).

Conclusion on efficacy:
These data suggest haloperidol efficacy in children with autistic disorder or PDD on some symptoms. However, these studies are old, mostly crossover, included children from 2 to 16 year age old, no data by age range was provided except two studies (Campbell and Cohen) which are contradictory: haloperidol was efficacious in children above 4.5 year old in Campbell study and in the more older children (> 4.5 years) in Cohen study.
Furthermore results are contradictory across studies and do not permit to well define the core symptoms improved with haloperidol.
During the preliminary assessment report, it was asked to the MAH to provide and discuss several data. The global analysis of the MAH is light and does not permit to well define the aimed symptoms, the paediatric population (diagnosis and age range) who may benefit from haloperidol treatment and the posology. The MAH response is not satisfactory

V.2 Safety

Safety data from clinical trials
For each term, the total frequency was calculated using the data from 9 placebo-controlled trials. These studies included a total of 283 patients on haloperidol and 282 on placebo. Six of these 9 studies have a crossover design, so the same patients had different periods on placebo and haloperidol. Frequencies in children were compared to those in adults. The most adverse events reported were extrapyramidal symptoms and sedation.

Table 1. Adverse events reported by ≥1% of haloperidol-treated subjects in 9 placebo-controlled clinical trials in children and adolescents compared to the frequencies of these terms as presented in the CCDS for adults.

	Pediatric trials		CCDS (adult population)	
	HAL%	PBO%	HAL%	PBO%
Extrapyramidal symptoms				
Dystonia	9.9	0.4	6.3	0.4
Extrapyramidal disorder	6.4	0.4	34.2	8.5
Tremor	4.2	1.1	8.1	3.6
Akathisia	3.9	0.0	2.9	NA[a]
Drooling	3.2	0.8	Not included	
Dyskinesia	2.1	3.8	2.5	NA[a]
Parkinsonism	2.1	0.0	<1	NA[c]
Hypokinesia	2.1	0.8	2.2	NA[a]
Cogwheel rigidity	0.7	0.0	Not included	
Gait disturbance	0.7	0.0	<1	NA[c]
Muscle rigidity	0.4	0.0	<1	NA[c]
Sedation	33.6	2.1	<1	NA[c]
Somnolence	6.7	1.1	5.3	1.1
Irritability	6.7	8.9	Not included	
Lethargy	4.2	0.0	Not included	
Decreased appetite	2.5	3.5	Not included	
Insomnia	3.2	3.2	>10	NA[b]
Depression	2.8	0.3	1-10	NA[b]
Dizziness	1.8	0.7	4.8	NA[a]
Nausea	1.4	0.4	1-10	NA[b]
Salivary hypersecretion	1.4	0.4	1.2	0.7
Pallor	1.1	0.0	Not included	

[a]AE reported in active comparator clinical trials
[b]AE identified during postmarketing experience [incidence estimated in either an epidemiology study or in clinical trial(s)]
[c]AE reported by <1% of haloperidol treated subjects in either placebo- or comparator-controlled clinical trials

Conclusion on safety:
The overall safety profile of haloperidol is well known. The most adverse events reported are related to extrapyramidal symptoms and sedation.

VI. RAPPORTEUR'S OVERALL CONCLUSION

Austistic disorder and pervasive developmental disorder are associated with a number of specific core symptoms with varying degrees.
When behavioural interventions are not fully effective, pharmacological treatment are often considered.
Most commonly, antipsychotics are used in alleviating mood and behavioural disturbances characterized by irritability, aggression, self-injury and agitation[b].
Short-term antipsychotic treatment in children should be an integral part of a more comprehensive treatment program, including psychosocial and educational intervention. Antipsychotics should be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of psychiatry disease of children and adolescents.

Haloperidol has been shown to be efficacious, with careful dose administration, for treating several of the behavioural symptoms associated with autism[c], particularly withdrawal, stereotypy, irritability and hyperactivity.

[b] Posey D.J. and al, Antipsychotics in the treatment of autism. The Journal of clinical investigation, Vol118, N1, Jan 2008.

The current role of haloperidol is limited due to the risk of extrapyramidal symptoms, especially tardive dyskinesia. Because of this, atypical antipsychotics are more commonly used, even if no atypical antipsychotic is approved in children with pervasive developmental disorder in Europe. However, safety concerns are also associated with atypical antipsychotics (weight gain and associated metabolic problems, hyper or hypoprolactinemia, sedation, adverse cognitive effects and extrapyramidal symptoms to a lesser extent than typical antipsychotic).

There is a real need of short-term treatment in children with austistic disorder and pervasive developmental disorder of symptoms as irritability, aggression, self-injury or agitation, which could disturb psychosocial and educational intervention.

Currently, haloperidol is indicated in children "as psychomotor anti-agitation agent: disorders of behaviour and character in children, especially when associated with hyperactivity and aggression and particularly in the context of autistic syndromes" in 10 Member States, a recommended dosage in children is available into section 4.2 in 5 Member States.
Haloperidol is a typical antipsychotic with a long used experience.

However, the current dossier provided by the MAH did not permit to well define the aimed symptoms and paediatric population (diagnosis and age range) who may benefit from haloperidol treatment and to recommend a well-defined posology.
On the other hand, post-marketing data confirm the risk of Extrapyramidal symptoms, sedation, altered state of consciousness and neuroleptic malignant syndrome.

As stated on recommendations on submission and assessment in paediatric worksharing, Dec 2009, "*it is not the aim of Article 45 or 46 procedure to remove existing paediatric indications for products which are already in clinical use in particular member states. Removal indications should be considered by individual member states unless there has been prior agreement by CMDh or through another regulatory procedure*". We suggest that haloperidol could be included on the list of the future SPC harmonisation and that this review could be performed via an article 30 procedure.

VII. FINAL RAPPORTEUR'S RECOMMENDATION

On the basis of the submitted data, with rather old studies, no formal recommendation on indications could be made.
However, it is not the aim of the paediatric worksharing procedure to remove paediatric indication.
We suggest that haloperidol could be included on the list of the future SPC harmonisation and that this review could be performed via an appropriate regulatory procedure.

The Rapporteur recommends changing the SmPC as follows:

4.4 Special Warnings and Special Precautions for Use

~~None~~

[c] Malone R.P. and al, the role of antipsychotics in the management of behavioural symptoms in children and adolescents with autism. Drugs, 2009 ;69(5) :535-548.

Available safety data in the paediatric population indicate a risk of extrapyramidal symptoms, including tardive dyskinesia, and sedation. No long-term safety data are available.

MAHs are thus requested to submit type IB variations to update the Product Information of haloperidol-containing medicinal products accordingly.

With regard to current paediatric indications approved in Member States, as stated on recommendations on submission and assessment in paediatric worksharing, Dec 2009, "*it is not the aim of Article 45 or 46 procedure to remove existing paediatric indications for products which are already in clinical use in particular member states. Removal indications should be considered by individual member states unless there has been prior agreement by CMDh or through another regulatory procedure*".
Paediatric indications may be maintained in MSs where they are already approved in the national SmPCs but no recommendations can be made as a result of the data submitted through this procedure.

In line with these changes, the corresponding sections of the PIL should be updated as follows:

2. What you need to know before you <take> <use> X
Warnings and precautions
Available safety data in the paediatric population indicate a risk of extrapyramidal symptoms, including tardive dyskinesia (involuntary, repetitive body movements), and sedation. No long-term safety data are available.

VIII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of the medicinal product	Strength	Pharmaceutical form
Janssen-Cilag	Haldol	1milligram	Tablet
Janssen-Cilag	Haldol	2 milligrams	Tablet
Janssen-Cilag	Haldol	5 milligrams	Tablet
Janssen-Cilag	Haldol	10 milligrams	Tablet
Janssen-Cilag	Haldol	20 milligrams	Tablet
Janssen-Cilag	Haldol	2 milligrams/millilitre	Oral solution
Janssen-Cilag	Haldol	0.5 milligrams/millilitre	Oral solution

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