



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 April 2008

DROLEPTAN 2.5 mg/1 mL, solution for injection (IV)
B/10 - CIP 561 122-8

Requested by PROSTRAKAN PHARMA

Droperidol
List I
For hospital use only

Marketing authorisation (MA) date: 11 September 1998
09 October 2007 (extension of indication)

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the extension of indication:

“Prevention of postoperative nausea and vomiting (PONV) in adults with a moderate to severe risk of PONV, in other words with at least two risk factors on the simplified Apfel score”,

and

“Prevention of postoperative nausea and vomiting in children over 2 years old with a moderate to severe risk of PONV as a second-line treatment and in the context of a multi-faceted management approach”.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Droperidol

1.2. Indication

In adults

- **Prevention of postoperative nausea and vomiting (PONV) in adults with a moderate to severe risk of PONV, in other words with at least two risk factors on the simplified Apfel score.**
- Treatment of postoperative nausea and vomiting.
- Prevention of nausea and vomiting induced by morphine derivatives during postoperative patient-controlled analgesia.

In children

- **Prevention of postoperative nausea and vomiting in children over 2 years old with a moderate to severe risk of PONV as a second-line treatment and in the context of a multi-faceted management approach.**
- Treatment of postoperative nausea and vomiting.

1.3. Dose

Prevention of postoperative nausea and vomiting:

- o in adults

between 0.625 mg and 1.25 mg, given intravenously, 30 minutes before the end of the surgical procedure.

- o In children

between 0.020 and 0.050 mg/kg, given intravenously, 30 minutes before the end of the surgical procedure.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

N	Nervous system
N05	Psycholeptics
N05A	Antipsychotics
N05AD	Butyrophenone derivatives
N05AD08	Droperidol

2.2. Medicines in the same therapeutic category

There are no other medicinal products with this indication in the neuroleptic class.

2.3. Medicines with a similar therapeutic aim

In adults

EMEND (aprepitant)

ONDANSETRON FAULDING (ondansetron)

In children

ZOPHREN (ondansetron) and generics, indicated for treatment of children over one month old

3 ANALYSIS OF AVAILABLE DATA

Droperidol has been used in humans for over 40 years. The clinical section of the marketing authorisation dossier consisted of bibliographical data (“well-established medical use”). The dossier submitted by the manufacturer relies on bibliographical data. It consists of 3 efficacy studies (two in adults, one in children) and safety data.

3.1. Efficacy

3.1.1. Studies in adults

FORTNEY study, 1998¹

This was a combined analysis of two controlled, randomised double-blind studies comparing droperidol (0.625 and 1.25 mg), ondansetron and placebo in 2061 patients undergoing surgery, with most patients undergoing gynaecological surgery.

The primary endpoint was the proportion of patients experiencing complete control of vomiting (no vomiting and no need for rescue treatment) for 2 hours and 24 hours after the procedure.

Table 1: Results for primary endpoint

		Placebo	Droperidol 0.625mg	IV Droperidol 1.25mg	IV Ondansetron 4mg
Complete response (0-2h)	Study 1	47% (121/256)	60% (153/256)	72% (182/253)	62% (159/257)
	Study 2	45% (115/254)	65% (167/256)	66% (166/252)	62% (158/253)
	Combined analysis	46% (236/510)	63% * (320/512)	69% *‡ (348/505)	62% * (317/510)
Complete response (0-24h)	Study 1	36% (93/255)	45% (115/253)	60% (152/252)	52% (133/254)
	Study 2	37% (93/253)	50% (129/256)	51% (128/251)	55% (137/251)
	Combined analysis	36% (186/508)	48% * (244/509)	56% *# (280/503)	53% * (270/505)

*p<0.05 (versus placebo)

#p<0.05 (versus Droperidol 0.625mg)

‡p<0.05 (versus Ondansetron 4mg)

¹ Fortney JT, Gan TJ, Graczyk S, Wetchler B, Melson T & al, A Comparison of the Efficacy, Safety, and Patient Satisfaction of Ondansetron Versus Droperidol as Antiemetics for Elective Outpatient Surgical Procedures, Anesth Analg 1998;86:731-8

The proportion of patients with a complete response was significantly higher in the “treatment” groups than in the placebo group. However, the authors did not provide confidence intervals, therefore the clinical relevance of the size of the effect cannot be evaluated.

Apfel study, 2004²

A randomised controlled trial versus "no treatment", carried out using factorial analysis, that evaluated the efficacy of several medicinal products (including droperidol) in 5199 patients at risk of PONV following surgery.

A significant reduction in the incidence of PONV (primary endpoint) was observed after administration of droperidol, with a risk reduction of 24.5% (95% CI [-30.2; -18.4], $p < 0.001$) which was comparable to that achieved with ondansetron and dexamethasone.

In addition, efficacy was greater in patients at high risk for PONV (at least 3 risk factors on the simplified Apfel score) when treatments were given in combination.

3.1.2. Study in children

Shende 2001 study³

Phase III controlled, randomised, double-blind study comparing droperidol, ondansetron, droperidol+ondansetron given as combination and placebo in 240 children who had undergone strabismus surgery.

The study design consisted of 4 groups (placebo, droperidol 25 µg/kg, ondansetron 150 µg/kg and droperidol 15 µg/kg + ondansetron 100 µg/kg).

The primary endpoint of the study was the incidence of PONV during the 24 hours following surgery.

Table 1: Results for primary endpoint

	Placebo (n=60)	Droperidol (n=60)	Ondansetron (n=60)	Droperidol + Ondansetron (n=60)
Incidence of PONV				
0-2h	35%	23%	18%	8% *
0-24h	62.5%	31.6% *	36.6% *	13.3% *.#.‡

* $p < 0.05$ (versus placebo)

$p < 0.05$ (versus Droperidol)

‡ $p < 0.05$ (versus Ondansetron)

Depending on the groups, only 5-15% of patients had a history of PONV.

The incidence of PONV during the first 24 hours was significantly lower in the “treatment” groups than in the placebo group.

In addition, the results showed that a combination of Droperidol + Ondansetron was significantly greater than Ondansetron alone.

However, the authors did not provide confidence intervals, therefore the clinical relevance of the size of the effect cannot be evaluated.

² Apfel C, Korttila K, Abdalla M, Kerger H, Turan A & al, A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting, N Engl J Med 2004;350:2441-51.

³ Shende D, Barthi N, Kathirvel S, Madan R, Combination of droperidol and ondansetron reduces PONV after pediatric strabismus surgery more than single drug therapy, Acta Anaesthesiol Scand 2001; 45: 756–760

3.2. Adverse events

Four safety studies have been provided by the manufacturer^{4, 5, 6, 7}.

Results of these studies suggest that at the low doses used in prevention of PONV, prolongation of QT interval caused by droperidol appears to be comparable to that observed in 5-HT3 antagonists.

According to the SPC, injectable droperidol causes a dose-dependent prolongation of QT interval. This effect is known to increase the risk of occurrence of serious ventricular rhythmic disturbances such as potentially fatal torsades de pointes and ventricular tachycardia, and the effect is increased in the presence of bradycardia, hypokalaemia, or congenital or acquired (medication that increases QT interval) long QT syndrome.

However, the vast majority of reported events involved doses of more than 25 mg, which is 20 times the recommended maximum dose for adults for prevention of PONV (1.25 mg).

Nevertheless, the SPC states that *“in patients with actual or potential risk of cardiac arrhythmia, an alternative to droperidol should be favoured when administering preventative treatment for PONV⁸”*.

In addition, droperidol can cause haematological, autonomic nervous system, metabolic (weight gain, hyperglycaemia etc) and neuropsychological disorders (sedation, dyskinesia, extrapyramidal syndrome, neuroleptic malignant syndrome etc).

3.3. Conclusion

In adults

Results observed for droperidol as a prophylactic treatment for PONV were superior to those observed for placebo, and were generally comparable to those observed for ondansetron or dexamethasone. No controlled study involving aprepitant is currently available.

At the low doses used in prevention of PONV, the safety profile seems acceptable.

In children

Droperidol has been shown to be significantly more effective than placebo in prevention of postoperative vomiting. According to the study provided, the effect is greater if dual therapy with ondansetron is used.

Its overall safety profile seems acceptable for use as a second-line therapy as part of a multi-faceted management approach.

⁴ White. Effect of Low-dose Droperidol on the QT Interval during and after General Anesthesia. *Anesthesiology* 2005; 102:1101–5

⁵ Charbit. Prolongation of QTc Interval after Postoperative Nausea and Vomiting Treatment by Droperidol or Ondansetron. *Anesthesiology* 2005; 102:1094-1100

⁶ Leslie et Gan. Meta-Analysis of the Safety of 5-HT3 Antagonists with Dexamethasone or Droperidol for Prevention of PONV. *The Annals of Pharmacotherapy* 2006 May; Volume 40

⁷ Nuttall. Does Low-dose Droperidol Administration Increase the Risk of Drug-induced QT Prolongation and Torsade de Pointes in the General Surgical Population? *Anesthesiology* 2007; 107:531-6

⁸ Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD004125. DOI: 10.1002/14651858.CD004125.pub2.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In adults

Postoperative nausea and vomiting are disabling and result in a marked deterioration in quality of life.

This product is a preventative treatment.

The efficacy/adverse reactions ratio for this medicinal product is high.

This medicinal product is a first-line therapy.

There are alternative treatments.

Public health benefit

Postoperative nausea and vomiting can lead to postoperative complications and reduces patient quality of life. However, the symptoms are transient, short in duration, and are not life-threatening. They represent a minor public health burden.

Postoperative nausea and vomiting are not an identified public health priority.

Given the available data, droperidol is not expected to have an additional effect in terms of improvements to quality of life or reduction in morbidity linked to **postoperative nausea and vomiting** in comparison with current methods of management.

Consequently, given the current knowledge of the subject, DROLEPTAN is not expected to give public health benefit in this indication.

The actual benefit of this product is substantial.

In children

Postoperative nausea and vomiting are disabling and result in a marked deterioration in quality of life.

This product is a preventative treatment.

The efficacy/adverse reactions ratio for this medicinal product is high.

This product is a second-line medication *in the context of a multi-faceted management approach*.

There are alternative treatments.

Public health benefit

Postoperative nausea and vomiting can lead to postoperative complications and reduces patient quality of life. However, the symptoms are transient, short in duration, and are not life-threatening. They represent a minor public health burden.

Although there is a need to improve therapeutic management of postoperative vomiting in paediatric practice, **postoperative nausea and vomiting** do not represent an identified public health priority.

Given the available data, droperidol is not expected to have an additional effect in terms of improvements to quality of life or reduction in morbidity linked to **postoperative nausea and vomiting** in comparison with current methods of management.

Consequently, given the current knowledge of the subject, DROLEPTAN is not expected to give public health benefit in this indication.

The actual benefit of this product is substantial.

4.2. Improvement in actual benefit

In adults as a first-line therapy and in children over two years old as a second-line therapy as part of a multi-faceted management approach, DROLEPTAN does not provide an improvement in actual benefit (IAB V) to the strategy for prevention of **postoperative nausea and vomiting** in patients with moderate to severe risk (at least two risk factors on the simplified Apfel score).

4.3. Therapeutic use

In adults

According to a meta-analysis by the Cochrane Collaboration Ref 8, eight products (cyclizine, droperidol, granisetron, metoclopramide, ondansetron, tropisetron, dolasetron and dexamethasone) have been shown to be effective compared with placebo in the prevention of postoperative nausea and vomiting. However, it has not proved possible to rank these treatments with respect to each other.

Use of a score to predict the risk of PONV, such as the Apfel score⁹, which has been validated in France¹⁰, enables at-risk patients to be identified, and an antiemetic prevention strategy to be implemented, depending on the level of risk. The simplified Apfel score consists of 4 predictive factors:

- 1) female sex
- 2) non-smoker
- 3) history of PONV or travel-sickness
- 4) administration of morphine postoperatively

Presence of 0, 1, 2, 3 or 4 of these factors is associated with incidence of PONV of 10%, 20%, 40%, 60% and 80%.

The available guidelines¹¹ do not recommend prophylactic antiemetic treatment for patients at low risk of PONV (as the risk/benefit ratio is low). Such treatment must be reserved for patients at moderate to severe risk of PONV (at least two risk factors according to the Apfel score). In high-risk patients, the guidelines suggest using a combination of antiemetics from different pharmacological classes.

DROLEPTAN IV is an additional therapy to be used in the management strategy for patients at moderate to severe risk of nausea and vomiting after a surgical procedure (at least 2 risk factors on Apfel score). In patients at actual or potential risk for heart rhythm disorders, an alternative to droperidol should be sought.

In children

The incidence of postoperative vomiting is twice as high in children as it is in adults. There is no validated predictive scoring method that can identify at-risk patient groups in children, as there is in adults. PONV treatment must therefore take several factors into account: patient risk factors (age, type and duration of surgery, anaesthesia used, history of PONV) and the risk of associated complications (rupture of sutures, repeat bleeding, inhalation of gastric fluid etc).

⁹ Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anaesthesiology*. 1999;91: 693-700.

¹⁰ Pierre S., Benais H., Pouymayou J. La cotation d'Apfel simplifiée peut prédire favorablement le risque de nausées et de vomissements postopératoires [*The simplified Apfel score can positively predict the risk of postoperative nausea and vomiting*]. *Can J Anaesth*. 2002;49 :237-42.

¹¹ Gan TJ et al. Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg* 2003;97:62-71

The available guidelines do not recommend prophylactic antiemetic treatment for patients at low risk of PONV (< 2 risk factors using the Apfel score) because of the low risk/benefit ratio.

Given its toleration profile (in particular sedation and extrapyramidal symptoms), DROLEPTAN IV should be used as a second-line treatment *as part of a multi-faceted management approach* in the treatment strategy for children aged over 2 years with a moderate to severe risk of PONV.

4.4. Target Population

In adults

The target population for DROLEPTAN IV is the population of patients undergoing a surgical procedure who are identified as being at risk of **postoperative nausea and vomiting** based on the simplified Apfel score (at least two risk factors).

In the absence of precise epidemiological data, an estimate of the target population can be obtained using the number of surgical patients at risk of PONV.

List of surgical procedures at risk of PONV
Source: PMSI 2004 – public/private

Type of surgery	Total procedures CDAM-CCAM (French surgical procedure classifications)
Digestive system	1,049,109
Gynaecology (ovaries, Fallopian tubes, uterus, sex change)	432,813
Urinary system (bladder, kidney)	210,658
ENT surgery (nose, throat, inner and middle ear, thyroid)	309,780
Prostate	69,799
Breast	168,224
Eye (strabismus)	15,027
Neurosurgery (head)	32,522
Orthopaedics (shoulder surgery)	12,300
Total	2,300,232

According to PMSI data (French computerised medical data), 2.3 million patients underwent surgical procedures at risk of PONV in 2004.

The generally accepted risk of PONV is 30/100.

The target population can therefore be estimated as 700,000 patients per year.

However, given the many contraindications to droperidol, this figure is an upper limit.

In children

In the Committee's opinion dated 9 May 2007 concerning ZOPHREN, a first-line prophylactic treatment for patients at moderate to severe risk of PONV, the target population was estimated at around 200,000 patients.

We do not currently have any epidemiological data which could provide information on the number of children requiring second-line treatment (if ondansetron is contraindicated or poorly tolerated, or if other treatment has failed). However, considering the estimated target population in adults, the target population in children must be negligible.

Overall, the target population in these indications would be a maximum of 700,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the extension of indication and at the posology of the MA.