

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

**Taxol
Paclitaxel**

NO/W/0003/pdWS

**Marketing Authorisation Holder:
Bristol-Myers Squibb**

Rapporteur:	NO
Finalisation procedure	29 December 2009
Date of finalisation of PAR	16 April 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Taxol
INN (or common name) of the active substance(s):	Paclitaxel
MAH:	Bristol-Myers Squibb
Pharmaco-therapeutic group (ATC Code):	L01CD01
Pharmaceutical form(s) and strength(s):	Concentrate for solution for infusion 6 mg/ml

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I. EXECUTIVE SUMMARY

Paclitaxel is indicated for the treatment of breast cancer, non-small cell lung cancer, ovarian cancer and AIDS-related Kaposi's sarcoma through national procedures and mutual recognition procedure. There are no paediatric indications for paclitaxel.

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

II. RECOMMENDATION

The Rapporteur considers the data on paclitaxel insufficient to give any advice on paediatric use. The MAH has proposed an amendment to the SmPC section 4.2 which is endorsed.

Amendment of section 4.2 of the SmPC: *Paediatric use: TAXOL is not recommended for use in children below 18 years due to lack of data on safety and efficacy*

III. INTRODUCTION

The MAH Bristol-Myers Squibb submitted one paediatric study for paclitaxel, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short expert statement has also been provided by Bristol-Myers Squibb.

The MAH has proposed the following regulatory action:

Amendment of section 4.2 of the SmPC: *Paediatric use: TAXOL is not recommended for use in children below 18 years due to lack of data on safety and efficacy.*

IV. SCIENTIFIC DISCUSSION

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

There is only one formulation of paclitaxel available from Bristol-Myers Squibb, i.e. the 6 mg/ml concentrate for solution for infusion was used in the submitted study. In addition to paclitaxel, this formulation contains poly-oxy-ethylated castor oil (Cremophor EL) as well as ethanol.

In 2008 a new formulation of paclitaxel, Abraxane (Abraxis BioScience Ltd.) received marketing authorisation through the centralised procedure. Abraxane contains human serum albumin-paclitaxel nanoparticles, where paclitaxel is present in a non-crystalline, amorphous state. Albumin is known to mediate endothelial transcytosis of plasma constituents and in vitro studies demonstrated that the presence of albumin enhances transport of paclitaxel across endothelial cells. Abraxane does not contain Cremophor EL and ethanol. The nano-formulation is considered a new active substance, and is therefore not included in this procedure.

IV.2 Non-clinical aspects

No non-clinical documentation has been provided.

IV.3 Clinical aspects

1. Introduction

The MAH has submitted one literature reference, an article by Doz et al published in the British Journal of Cancer in 2001: *Phase I trial and pharmacological study of a 3-hour paclitaxel infusion in children with refractory solid tumour: a SFOP study*.

A PubMed search revealed several publications with paclitaxel in children. A review article published in 2006 (André and Meille, Cancer treatment reviews 2006), covers four phase I studies, with paclitaxel monotherapy in children, including the submitted study, as well as two phase II studies.

Assessor's comment

The statement from Bristol-Myers Squibb only covers the submitted study, ie. Doz et al 2001. The MAH has not given any information on whether any paediatric studies have been reviewed by the authorities in the past.

To give a more comprehensive review, some of the articles which were referred to in the review article by André and Meille are briefly described below. Studies performed in 2008 or later, are left out of this assessment.

2. Clinical studies

Phase I

Doz et al, 2001

Phase I trial and pharmacological study of a 3-hour paclitaxel infusion in children with refractory solid tumour: a SFOP study, Doz et al. British Journal of Cancer (2001) 84(5), 604-610.

The aim of this study was to determine the dose-limiting toxicity, maximum tolerated dose and pharmacokinetics of paclitaxel in children with refractory solid tumours when administered as a 3-hour infusion. Some clinical data in adults indicate that a 3-hour short-term infusion might offer equivalent anti-tumour efficacy as a 24-hour infusion with reduced haematological toxicity and without increasing the risk of hypersensitivity (Eisenhower et al, 1994).

The study included 17 patients between 1.6 and 19 years (median 9) with malignant solid tumours, refractory to at least two lines of conventional therapies. Premedication was performed using dexamethasone (0.25 mg/kg, 12 and 6 hours before infusion) and dexchlorpheniramine (2.5 to 5 mg according to age) 30 minutes before infusion. The starting dose of paclitaxel was 240 mg/m² taking into account the recommended dose in adults for short-term infusion (Schiller et al, 1994) as well as the recommended dose in children for 24 hours infusion (Hurwitz et al, 1993). Dose escalation was planned with 20% increments: second step 290 mg/m², third step 350 mg/m², and fourth step 420 mg/m². A minimum of 3 patients were included at each step. There was no inpatient dose escalation.

Grade IV non-haematological dose-limiting toxicity was observed in three patients. One of the patients in the 420 mg/m² had an anaphylactic reaction and died of multiorgan failure 12 hours after the start of the first course of paclitaxel. The other two developed transitory coma, one of them few minutes after the infusion of 420 mg/m², and the other after the second course of 350 mg/m².

The observed haematological toxicity was not dose-limiting. Neutropenia (grade III and IV) occurred seven times and leukopenia (grade III) occurred five times across the dose range 240-350 mg/m², while there were there were no cases of thrombocytopenia.

Tumour response was to be evaluated after the second course. One patient with embryonal rhabdomyosarcoma had a partial response and one patient with alveolar rhabdomyosarcoma had stable disease; both were treated with 350 mg/m² and both had to stop treatment due to adverse events. Two patients did not have disease progression after the first course, but treatment had to be stopped due to severe toxicity. The remaining patients had disease progression; ten after one course and two after two courses.

The pharmacokinetics of paclitaxel seemed non-linear with this regimen as clearance appeared to decrease as the dosage increased. This could be due to saturable distribution and elimination or entrapment of paclitaxel in its vehicle.

High plasma alcohol levels were found after infusion; C_{max} values ranged between 0.24 and 2.04 g/l. The levels of Cremophor EL ranged between 6.12 and 22.37 g/l. Severe neurological toxicity was observed in both patients with the highest concentrations of ethanol and Cremophor EL. Three of the four highest ethanol concentrations, above 1.45 g/l, were found in three patients with coma and somnolence.

The authors concluded that paclitaxel as a 3-hour infusion every three weeks can not be recommended to children due to dose-limiting neurological toxicity which could be attributed to both paclitaxel, ethanol and Cremophor EL.

Assessor's comment

In adults, a 3-hour infusion of paclitaxel is recommended in all indications. For the first-line treatment of ovarian cancer a 24-hour infusion is given as an alternative. The recommended dose for adults in the SmPC (Norway) is varying between 100 and 175 mg/m² depending on the length of the infusion and the indication. However, higher doses (225 mg/m²) are used according to the national register of cancer treatment in Norway. Schiller et al (1994) conducted a study to investigate the dose of paclitaxel when using a 3-hour infusion in adults. This mode of treatment was found to be acceptable at a dose level of 250 mg/m² with G-CSF support and 210 mg/m² without G-CSF support. The benefits of the 3-hour infusion were supported by other studies, e.g. Eisenhauer et al, 1994.

The Doz study concluded that a 3-hour infusion was unacceptable for the treatment of children in terms of toxicity. In addition, only limited response was observed. The pharmacokinetics of paclitaxel in a 3-hour infusion was found to be non-linear in children as it is for adults (SmPC for Taxol).

Hurwitz et al, 1993

This was a Phase I trial conducted to describe the principal toxicities and identify the maximum tolerated dose of paclitaxel administered as a 24-hour infusion every 21 days in children (median age 12 y, range 2-22y) with refractory solid tumours. The doses ranged from 200 to 420 mg/m², with no inpatient dose escalation. There were two patients with allergic reactions; both developed acute anaphylaxis during their second infusion at doses of 200 and 350 mg/m². Peripheral neuropathy appeared at doses ≥ 290 mg/m². Dose-limiting neurotoxicity occurred at 420 mg/m² in two patients; one patient had a tonic-clonic seizure and one had significant fine-motor and peripheral neuropathy. From this study the recommended dose of paclitaxel for Phase II trials was found to be 350 mg/m². Four out of 31 patients had response; one patient with papillary serous carcinoma had complete response, two had partial response and one had minimal response. Nine patients had stable disease.

Assessor's comment

The maximum tolerated dose for a 24-hour infusion in children was found to be 350 mg/m² in this study.

Hayashi et al, 2003

Hayashi et al investigated 3-hour infusions twice weekly in 16 children with refractory or recurrent solid tumours. Paclitaxel was increased from four to six doses every 21 to 28 days. The initial dose was 50 mg/m² and was increased in 25% increments. Neutropenia was the dose-limiting toxicity at 65 mg/m² twice weekly for three weeks every 28 days. The maximum tolerated dose of paclitaxel twice weekly for three weeks every 28 days was found to be 50 mg/m². No tumour responses were observed.

Assessor's comment

This study did not find a dosage for children with acceptable toxicity.

Woo et al, 1999

This was a study to investigate the use of maximum tolerated systemic exposure (MTSE) for anticancer drugs instead of maximum tolerated dose (MTD) in Phase I studies. Paclitaxel was chosen to test the MTSE strategy because of its wide interpatient pharmacokinetic variability. Seven children with refractory leukaemia were included in the study. Mucositis was the dose limiting toxicity and occurred at lower AUCs than expected from studies in children with solid tumours. Six patients had worsening of their leukaemia within 20 days. Only one patient received a second course of treatment; the disease progressed rapidly after the second course.

Assessor's comment

Based on this small study, paclitaxel does not seem to have a place in the treatment of children with refractory leukaemia as the efficacy is limited and the toxicity substantial. However, these patients were highly refractory. This could explain the high susceptibility to gastrointestinal toxicity as well as no tumour response.

Phase II**Hurwitz et al, 2001**

This was a study in children (73) with progressing or relapsing brain tumours of different histologies who were treated with paclitaxel 350 mg/m² over 24 hours every three weeks. One complete response in a patient with medulloblastoma and three partial responses in patients with brain tumours of different histological subtypes were observed; 22 patients had stable disease. There were 45 episodes of more than grade 3 neutropenia and 18 episodes of more than grade 3 thrombocytopenia.

Assessor's comment

The response rate was low in this phase II study. It is suggested that this poor response is partly due to increased metabolism of paclitaxel since known inducers of cytochrome P 450 were used concomitantly with paclitaxel, i.e. phenytoin and corticosteroids. Higher numbers of partial responses with paclitaxel have been found in adults with brain tumours. The reason for this could be that the adult studies were limited to patients with a few histological subtypes. Alternative treatment options such as temozolomide makes further investigations of paclitaxel in the treatment of brain tumours less interesting.

Kretschmar et al, 2004

This study investigated paclitaxel, topotecan and topotecan-cyclophosphamide in children with untreated stage IV neuroblastoma. Thirty-three patients received paclitaxel 350 mg/m² over 24 hours every two or three weeks depending on the neutrophil count. The patients were evaluated after two courses of treatment, and then received intensive induction therapy and bone marrow transplantation. Two patients had grade 3 and two had grade 4 allergic reactions to paclitaxel. Sixteen had grade 3 to 4 neutropenia and six had grade 3 to 4 thrombocytopenia. The response rate for paclitaxel was 25%; one patient had complete response, five had partial response and two had mixed response. In the topotecan and topotecan-cyclophosphamide groups, the response rates were 67% and 76%, respectively.

Assessor's comment

In neuroblastomas paclitaxel gave a response rate of 25% after two courses. However, with the good response seen with other therapies, e.g. carboplatin and ifosfamide, in addition to topotecan and topotecan-cyclophosphamide, paclitaxel does not seem to have a place in the treatment of neuroblastomas in children.

3. Discussion on clinical aspects

In the study by Hurwitz et al (1993), 24-hour regimens of paclitaxel with up to 350 mg/m² seem to have acceptable toxicity profiles in children. Three-hour infusions of up to 250 mg/m² paclitaxel have shown acceptable toxicity in adults. However, as shown by Doz et al, 3-hour infusions do not seem to be acceptable in the treatment of children due to toxicity. The grade III and IV acute toxicities were encountered with the higher doses of paclitaxel, i.e. 350 mg/m² and 420 mg/m². The toxicity could be caused by both paclitaxel and the excipients. The use of relatively high doses of paclitaxel in the studies limited the number of courses given, which could partly explain the low response rates obtained. In addition, the patients were heavily pretreated.

The phase II study in children with brain tumours gave disappointing results, while the study in neuroblastomas was more promising with regard to efficacy, with a response rate of 25%. However, as pointed out by the authors, other therapies give much higher response rates than paclitaxel in neuroblastomas. Both studies used the 24-hour regimen recommended by Hurwitz et al, i.e. 350 mg/m², every two or three weeks.

No phase III studies have been performed in children for any indication. With the results from the brain tumour study there seems to be less reason to go further with this indication. The same goes for the neuroblastoma indication as better alternatives exist. For children with leukaemia the toxicity of paclitaxel seems unmanageable. However, some of the children with solid tumours did respond to treatment and further studies with a manageable dosage regimen, such as the one recommended by Hurwitz et al, could be undertaken.

In conclusion, with the limited data available, paclitaxel cannot be recommended in children.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Given in the right dosage regimen, paclitaxel could have a place in paediatric cancers. However, with the limited data obtained so far, it is not possible to recommend any use in children. Thus the suggested amendment to section 4.2 of the SmPC is considered appropriate.

Amendment of section 4.2 of the SmPC: *Paediatric use: TAXOL is not recommended for use in children below 18 years due to lack of data on safety and efficacy*

➤ Recommendation

Type IB variation to be requested from the MAH by 2010-07.12

VI. LIST OF REFERENCES

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