

# Paediatric Public Assessment Report

## EU Work Sharing Procedure – Assessment of Paediatric Data

**Paraplatin**  
**INN carboplatin**

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

<b>Rapporteur:</b>	Netherlands
<b>Co-Rapporteur:</b>	Sweden
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## I. INTRODUCTION

In recent years, both US and EU have taken initiatives to increase the number of studies in children. EU is still in the process of finalising a regulation. FDA, however, has already received data for many products on the use in children.

Most of the studies, conducted in the paediatric population, are a result of the new FDA approach and the study reports are submitted to the FDA for review. The aim of the “EU work sharing project assessment of paediatric data” is to make the paediatric data, already submitted to FDA, available for the European health professionals. The aim is to achieve a harmonised decision between all MSs in the Work sharing procedure. The main principle is that two Member States assess the data and prepare an assessment report for the other Member States.

The application consists of two studies in children using the *combination* of Paraplatin and Irinotecan.

The available paediatric data were already submitted to the FDA in March 2004 and assessed on 29 September 2004, as “inadequate information” to support any label change.

The data were subsequently submitted (in December 2004) to the MHRA (in response to their request on 12 May 2004). The data were again not deemed adequate to support any label change.

The same data are submitted, on September 1<sup>st</sup>, 2005, to all EU Member States and Norway, Iceland and Liechtenstein, without any proposal for labelling changes. The Netherlands and Sweden act as rapporteurs for the current assessment.

### I.1 Scope of the assessment

Paraplatin/carboplatin is an anti-tumour agent whose predominant mechanism of action is believed to be mediated by binding to replicating DNA, causing single-strand breaks and cross-links. Previous studies have demonstrated activity against paediatric tumours, most notably in neuroblastoma and other brain tumours. However, the activity of carboplatin has only been demonstrated in Phase I and II studies, but not in Phase III studies. Still, carboplatin is frequently used in practice in paediatric, mostly CNS, tumours. Carboplatin is currently not indicated for paediatric tumours in Europe.

In Europe paraplatin is currently approved for the treatment of advanced carcinoma of the ovaries, small cell and non-small cell carcinoma of the lung, advanced head and neck carcinoma, and advanced carcinoma of the bladder. Paraplatin is not registered in The Netherlands anymore. However, several generics of carboplatin are on the market. In the Netherlands, carboplatin is only indicated for the treatment of patients with advanced or metastatic epithelial ovarian cancer.

Regarding this application, data from two paediatric studies have been submitted by the MAH as a request with the “EU work sharing project assessment of paediatric data”. The submitted data consists of a phase I dosing study with pharmacokinetic evaluation in order to establish the maximal tolerated dose (MTD) and the recommended Phase II dose (RPIID) (study CA124001), followed by a randomized non-comparative Phase II study (study CA124002). The activity of carboplatin was evaluated in combination with irinotecan.

A summary of the clinical program is shown in table 1.

Table 1: summary of the clinical program

Study	Design	Dosage	Evaluations
CA124001 Phase I study	multi-centre, open-label, single arm dose escalation phase I study, conducted between June 2001 and December 2003 in 28 patients (median age 8.5 years). Combination carboplatin every 3 weeks with irinotecan daily x5x2 every 3 weeks	Dosing schedule consisted of carboplatin administered every 21 days in combination with irinotecan administered daily x 10 days every 21 days (with growth factor support), according to the dose evaluation scheme represented in table 2.	Maximal Tolerated Dose (MTD)  Recommended Phase II Dose (RPIID)
CA124002 Phase II study	Study CA124002 was a multi-centre, open-label randomized, non-comparative study which was conducted between February 2003 and February 2004.  151 Patients (1-21 years). Stratification according to location of the primary tumour (CNS or non-CNS).	either carboplatin in combination with irinotecan (according to the RPIID established in study CA124001: carboplatin AUC 4mg/ml x min and irinotecan 12 mg/m <sup>2</sup> /day) or irinotecan as a single agent (20 mg/m <sup>2</sup> /day).	Comparison of the combination regimen carboplatin and irinotecan with irinotecan alone in terms of efficacy and safety.

## II. SCIENTIFIC DISCUSSION

### II.1 Quality aspects

Not applicable

### II.2 Non-clinical aspects

Not applicable

## II.3 Clinical aspects

Based on discussions with the FDA regarding the development of a clinical program to evaluate carboplatin in paediatric patients, the regimen to be evaluated for the paediatric program was to include the combination of carboplatin with irinotecan. Significant activity of carboplatin against a variety of paediatric tumours, most notably in neuroblastoma and brain tumours, has been reported. Single-agent irinotecan has shown significant antitumour activity in xenograft models of childhood tumours, including neuroblastoma, rhabdomyosarcoma, medulloblastoma, ependynoma and glioblastoma. Since these distinct cytotoxic drugs have different biological targets, modes of action, and mechanisms of resistance, together they are likely to be more effective, especially against refractory tumours.

The clinical program consisted of a phase I dosing study with pharmacokinetic evaluation in order to establish the maximal tolerated dose (MTD) and the recommended Phase II dose (RPIID) (study CA124001), followed by a randomized non-comparative Phase II study (study CA124002).

### Rapporteur's comment:

*In the literature carboplatin has been reported to have activity against a variety of paediatric tumours, most notably in neuroblastoma and brain tumours. However, the activity of carboplatin has only been demonstrated in Phase I and II studies, but not in Phase III studies. Still, carboplatin is frequently used in practice in paediatric, mostly CNS, tumours.*

*Carboplatin is currently not indicated for paediatric tumours in Europe. The current paediatric program, evaluating carboplatin in combination with irinotecan, including only Phase I and II studies, may not be enough to provide conclusive data to evaluate the value of carboplatin in the paediatric population.*

### II.3.1 Pharmacokinetics

#### Study design and objectives:

A **phase I study CA124001** and **one phase II study CA124002** were submitted which evaluated the combination of carboplatin every 3 weeks with irinotecan daily x 5 x 2 every 3 weeks. Only the phase I study included pharmacokinetic evaluation. The phase I study was a dose finding study with pharmacokinetic evaluation conducted in 28 patients (17 m, 11f) aged 1-21 (10<4y, 6 between 5-10, 12>11y) with refractory or relapsed solid tumours to establish the maximum tolerated dose (MTD). Both agents were administered intravenously and the carboplatin infusion (50 min) preceded the irinotecan infusion (60 min) on day1 of each cycle. The first dose level consisted of carboplatin given at target AUC of 4.0 mg/ml\*min, and irinotecan at 18 mg/m<sup>2</sup>/dose. Due to experienced toxicity of the combination, irinotecan was decreased to 12 mg/m<sup>2</sup>/day and the dose level of carboplatin could not be increased (in two patients carboplatin at target AUC of 5 mg/ml\*min was administered).

#### Methods:

On day 1 the patients received an approximately 50 minutes infusion of carboplatin followed by a 60 minutes infusion of irinotecan beginning exactly 60 minutes after the start of carboplatin infusion, followed by irinotecan doses on day 3, 5, 8, 10 and 12.

Plasma pharmacokinetics of ultrafiltrable platinum, irinotecan, SN.38 and APC (RPR-121056) were determined during the first cycle of treatment. Sampling schedule (pre-dose, 30 min, 48 min, 1 h 30 min, 2, 4, 6, 8 and 24 hours after start of carboplatin infusion. Pre-dose samples for irinotecan were obtained on the subsequent administration days.

Blood samples was withdrawn in tubes containing K<sub>3</sub>EDTA and immediately centrifuged to obtain plasma, part of which was immediately transferred to ultrafiltration device.

## Assays

Irinotecan, SN-38 and APC concentrations were determined by a validated HPLC-MS method. Plasma ultrafiltrate samples were assayed for platinum concentrations by a validated flameless atomic absorption method. The range of the standard curves in plasma were 5.01 to 401.15 ng/ml for irinotecan, 0.05 to 4.029 ng/ml for SN-38, 0.50 to 39.96 ng/ml for APC and 100 to 4000 ng/ml for platinum. The between run precision and within run precision <7.1 and 7.7% CV respectively and deviations from nominal < ±10.7% for all assays.

The pharmacokinetic analyses were performed using SAS, version 6.12 software package using standard non-compartmental methods.  $C_{max}$ ,  $t_{max}$ , MRT, and  $t_{1/2}$  were determined for Irinotecan, SN-38, APC and platinum. AUC was determined from 0-7 hours for Irinotecan and APC, from 0-23 hours for SN-38 and from 0-∞ for platinum. Total body clearance and  $V_{ss}$  were determined for irinotecan and ultrafilterable platinum. The pre-dose plasma concentrations of irinotecan and its metabolites on Days 3, 5, 8, 10, and 12 were evaluated for possible accumulation.

## Data

Blood samples were collected from 26 of the 28 patients enrolled in the study. Adequate concentration versus time profiles were available from 20 of the 28 patients for platinum and from 22 for irinotecan and its metabolites. Four different dosing groups were used. Carboplatin was adaptively dosed, based on the glomerular filtration rate (GFR) to achieve a target AUC of 4.0 mg.min/ml using the St. Jude Children's research Hospital (SJCRH) formula (modified version of the Calvert formula): carboplatin dose (mg/m<sup>2</sup>)= target AUC (mg/ml\*min) x[0.93 x GFR(ml/min/m<sup>2</sup>)+15].

If GFR was reported as ml/min the estimate was divided by body surface area and if reported as ml/min/1.73m<sup>2</sup> it was divided by 1.73.

Platinum pharmacokinetics was obtained from the following treatment groups;

I: 4.0 (min mg/ml) carboplatin and 18 mg/m<sup>2</sup> irinotecan (N=5)

II: 4.0 + 15 (N=5)

III: 4.0 +12 (N=8)

IV: 5.0 + 12 (N=2)

Irinotecan (and metabolites) pharmacokinetics was obtained from one more subject in each of treatment group II and III.

GFR is estimated from creatinine clearance by a 24 hour urine collection or radioisotopic determination by using e.g. <sup>99m</sup>Tc-DTPA.

In study CA124001, the plasma PK of ultrafilterable platinum, irinotecan, and two metabolites of irinotecan, SN-38 and APC (RPR-121056), were determined during Cycle 1 for all patients.

Ultrafilterable platinum was measured by atomic absorption spectroscopy over the concentration range of 100 to 4000 ng/ml.

## Results

Due to lack of an adequate number of samples, data from 8 patients (25-30%) were discarded for carboplatin PK evaluation as they could not be utilised in the non-compartmental pharmacokinetic analysis methodology. The mean ± standard deviation measured exposure to platinum from carboplatin for patients dosed with carboplatin AUC 4 was 2.64 ± 0.78 mg/ml\*min (range: 1.56 – 4.03 mg/mlxmin) as compared to the theoretical target of 4 mg/ml\*min. and for the two patients with target AUC of 5 the AUC<sub>0-∞</sub> were 2.12 and 3.20 respectively.

Irinotecan, SN-38, and APC were generally quantifiable through 7, 23, and 7 hours, respectively, after the start of the irinotecan infusion. Platinum was generally quantifiable through 8 hours after the start of the carboplatin infusion. The exposure of patients to lactones of irinotecan, SN-38, and APC in this study were consistent with values reported in a previous study of this protracted low-dose regimen.

Results for each treatment group are presented in table 2.

Table 2. Platinum pharmacokinetic parameter estimates by treatment group presented as geometric mean and total range (unless otherwise stated).

Parameter	Treatment group I 4.0 (min mg/ml) carboplatin and 18 mg/m <sup>2</sup> irinotecan (N=5)	Treatment group II (4.0 + 15)	Treatment group III (4.0 + 12)	Treatment group IV (5.0 + 12)
AUC <sub>0-∞</sub> (min mg/mL)	2.49 (1.82 – 3.58)	2.85 (1.86 – 3.74)	2.38 (1.56 – 4.03)	2.60 (2.12 – 3.20)
CL (L/h)	9.85 (7.19 – 15.97)	5.84 (2.61 -19.31)	9.42 (2.79 – 19.01)	7.95 (5.76 – 10.98)
C <sub>max</sub> (ng/mL)	16920 (9660* – 31700)	21137 (13400 – 27800)	18915 (11500 – 33400)	22137 (21400 – 22900)
V <sub>ss</sub> (L) (mean and SD)	33.57 (12.48)	15.43 (9.63)	20.73 (14.34)	17.48 (12.10)
MRT (h)	3.45 (1.58)	2.73 (1.87)	1.77 (0.37)	1.96 (0.58)
T <sub>1/2</sub>	4.61 (1.98)	2.86 (1.74)	1.57 (0.21)	1.92 (0.29)

\*Tmax 0.5 hour for one individual, for all others Tmax 0.8 hour

Co-Rapporteur's comment:

Even if this study material is very small and from a combination therapy study, it is worth noting that only one patient obtained the target AUC with the applied way of calculating the carboplatin dose. The file included a table with dosing errors during study. It would have been beneficial for the assessment of the study if the actual doses received and expected AUC from those doses would have been included in the table with individual pharmacokinetic estimates, preferably also including age. Irinotecan pharmacokinetics was not assessed in this report.

The pharmacokinetics material is too small to make any general conclusions that would result in changes to the SPC. It is however worth noting that only one patient obtained target AUC, suggesting that dose calculations based on the SJCRH formula is inadequate and further studies explaining interindividual variability in the paediatric population is of value. No attempt to correlate platinum pharmacokinetics to different demographic factors was done. It should also be noted that more data on paediatric pharmacokinetics are available in literature, where population pharmacokinetic models and dose individualisation techniques have been described, that has not been included or discussed in this application.

Rapporteur's comment:

In the literature carboplatin adaptive dosing based on GFR has been reported to result in less variation in AUC than based on dosing according to surface area. In the Calvert formula, GFR estimation is based on [51Cr]-EDTA measurement. Literature data indicate that substitution of the GFR by creatinine clearance measured by the 24-h method or calculated by the formula of Cockcroft and Gault may lead to systematic over- or under prediction. In this study, GFR is estimated from creatinine clearance by a 24 hour urine collection or by radioisotopic determination by using e.g. <sup>99m</sup>Tc-DTPA. From the data it is not clear which method is used in which patients to estimate the GFR. In this study the adaptive dosing of carboplatin based on GFR underestimated the dose required to achieve the target carboplatin AUC in paediatric patients treated concurrent irinotecan: mean measured carboplatin AUC was 2.6 mg/ml\*min as compared to target AUC of 4.0 mg/ml\*min. Only 25% of the measured carboplatin AUCs were within 25% of the target AUC of 4 mg/ml\*h respectively 5 mg/ml\*min. Furthermore, in about 20% of the patients the actual dose received differed more than 25% from the calculated dose. Therefore, it is difficult to reach definitive conclusions regarding PK and dosing for carboplatin based on the present data.

In order to enable to evaluate the present data better, the applicant was requested to present the data of the actually administered carboplatin AUC versus the measured AUC. Furthermore, the applicant was requested to indicate in which patients GFR estimation was based on 24h urine creatinine clearance or based on radioisotopic measurement and to explore the relation of the used GFR method with measured carboplatin AUC. The applicant was asked to discuss why the target carboplatin AUC

*of 4 mg/ml\*h has not been reached in this paediatric population and whether baseline characteristics could be identified to reduce the variability in carboplatin PK in paediatric patients.*

*Assessment of the response led to the following conclusions:*

*Bone marrow toxicity reported in this study suggests that an effective dose of carboplatin has been administered, but the AUC of carboplatin as measured platinum in plasma ultra filtrate was substantially below the predicted AUC as calculated from the actual dose administered by either the Calvert formula using creatinine clearance based on 24-h urine collection or SJCRH formula using GFR. The SJCRH formula and other different versions of the Calvert formula have shown to reduce the variability in the paediatric patients compared to dosing based on BSA but under- and overdosing has been reported may be due to the manner in which renal function is measured.. applicant considers the most likely cause of low values found for measured carboplatin AUC is inadequate sample collection and processing of the blood samples at the clinical sites. It is recognised that for accurate measurement of platinum rapid processing of blood to plasma ultra filtrate is necessary, although carboplatin is less sensitive than cisplatin as the rate of protein binding to plasma proteins is lower. Nevertheless, as the MAH can not guarantee an adequate collection and processing of the blood samples at the clinical sites, the data of this study can not be used to make any general conclusions regarding pharmacokinetics that would result in changes to the SPC. It should be noted, that the applicant is not seeking an indication for carboplatin in paediatric populations.*

*The applicant also argues that a posology recommendation for children cannot be given, as data from pharmacokinetic Study CA124001 are not reliable. Further, the literature shows that there is a large between patient variability in carboplatin AUC especially in the paediatric population. If a reliable measure of renal function is available for a patient, particularly if renal impairment is suspected, the use of dosing formula appears to offer an advantage over dosing based on surface area alone. This could be mentioned in section 5.2 of the SPC*

### II.3.2 Clinical efficacy

#### Main study(ies):

##### Phase I study CA124001

Study CA124001 was a multi-centre, open-label, single arm dose escalation study that included PK evaluation which was conducted between June 2001 and December 2003. The primary objective of the study was to establish the Maximal Tolerated Dose (MTD) and the Recommended Phase II Dose (RPIID) of carboplatin in combination with irinotecan (with growth factor support) to children with refractory solid tumours.

#### *Methods*

A total of 28 patients were enrolled with a median age of 8.5 years (range 1-21), the majority were male (60.7%) and white (64.3%). Patients with the following tumour types were enrolled: 4 neuroblastoma, 3 astrocytoma, 3 rhabdomyosarcoma, 2 medulloblastoma, and 16 other tumour types including hepatoblastoma and osteosarcoma.

Dosing schedule consisted of carboplatin administered every 21 days in combination with irinotecan administered daily x 10 days every 21 days (with growth factor support), according to the dose evaluation scheme represented in table 3.

**Table 3:** CA124001 Dose Evaluation scheme

Dose level	Carboplatin AUC (mg/ml x min)	Irinotecan (mg/m <sup>2</sup> /day x 5 for 2 wks)	Number of patients enrolled
-2a	5.0	12	3
-2	4.0	12	13
-1	4.0	15	6
1 (starting dose)	4.0	18	6

#### *Results*

The -2 dose level was identified as the MTD, as well as the RPIID. This dose level was expanded to a total of 13 children in order to confirm the safety of this dose for the Phase II study.

Although efficacy was not the primary objective of the study, each patient's best overall tumour response was assessed by the BMS Medical Team. Of the 28 patients in the study, 1 patient had a complete response (at dose level -2), 3 patients had a partial response (1 at dose level 1 and 2 at dose level -2), and 10 patients had stable disease (3 at dose level 1 and 7 at dose level -2).

## Phase II study CA124002

Study CA124002 was a multi-centre, open-label randomized, non-comparative study which was conducted between February 2003 and February 2004. Primary objective was to compare the combination regimen carboplatin and irinotecan with irinotecan alone in terms of efficacy and safety.

### Methods

Patients between 1 and 21 years with refractory solid tumours were randomized to receive either carboplatin in combination with irinotecan (according to the RPIID established in study CA124001: carboplatin AUC 4mg/ml x min and irinotecan 12 mg/m<sup>2</sup>/day) or irinotecan as a single agent (20 mg/m<sup>2</sup>/day). Within each treatment arm, patients were stratified according to location of the primary tumour (CNS or non-CNS).

A total of 151 patients were randomized, and 148 treated. The most common CNS tumour types were medulloblastomas (11 patients) and “other” tumour types (26 patients), and the most common non-CNS tumour types were osteosarcomas (19 patients) and “other” tumour types (19 patients). The BMS medical team reviewed tumour assessments and determined each patient’s best overall response.

### Results

There were 7 responders in the CNS group. One patient who received carboplatin in combination with irinotecan experienced a complete response. In both treatment arms, 3 patients experienced a PR.

There were 9 responders in the non-CNS group. Two patients who received irinotecan alone experienced a CR, while 7 patients (3 on combination therapy and 4 on irinotecan alone) experienced a PR.

**Table 4:** CA124002 Efficacy Results

	CNS tumours		Non-CNS tumours	
	Carboplatin+Irinotecan N=28	Irinotecan N=28	Carboplatin+Irinotecan N=47	Irinotecan N=48
CR+PR	4	3	3	6
Response rate (%) (95% CI)	14 (4-33)	11 (2-28)	6 (1-18)	13 (5-25)

***Rapporteur’s comment:***

*The efficacy data do not justify to include a treatment indication for the paediatric population.*

*The rationale of use of irinotecan (targeting topoisomerase I) stems from preclinical data from xenograft models. Moreover, topoisomerase I activity has been retrieved in neuroblastomas and medulloblastomas. In neuroblastoma, N-myc amplification, which is a factor of poor prognosis in children, was shown to be significantly associated with high levels of topoisomerase I.*

*However, the response rate of the combination therapy as compared to irinotecan alone do not show a clear benefit of the addition of carboplatin to irinotecan.*

Co-Rapporteur's comment:

*A few responses of limited duration were seen in the combination treatment dose finding study CA124001. A limited number of responses were observed across treatment arms in study CA124002. The numbers were similar between the groups. A comparison between the groups was not planned and it is difficult to assess the effect of carboplatin itself since there was no group with single agent carboplatin in the study and the irinotecan dose differed between the two groups. Responses ranged in duration from 1 month to 5 months. In two cases, there were responses of 5 or close to 5 months (one patient with pineoblastoma, group A and one patient with rhabdomyosarcoma group B). 9 of the 16 responding patients were censored for response duration at last tumour assessment date, making it difficult to draw any firm conclusions regarding response duration.*

### II.3.3 Clinical safety

The safety reports contain a comprehensive review and analysis of all pre- and post marketing reports in paediatric patients treated with carboplatin.

The report contains all adverse event reports from January 2003 (International Birth date) to October 2004 (data lock point)

In this period the MAH has received 327 paediatric reports from 30 different countries.

The MAH has submitted the requested documentation including two paediatrics study reports, an expert review and a safety summary (which has been submitted to the MHRA in December 2004, without any proposal for label change).

The FDA review of the data concerning carboplatin led to the recommendation not to add any information based on the paediatric studies conducted to the label

#### Adverse events

During the period under review the MAH could identify 327 paediatric reports of adverse events, which included carboplatin as a suspect or interactive drug. 135 reports were received from spontaneous sources world-wide, 128 were received from clinical trials. 267 were classified as serious and a fatal outcome was reported in 123 of the 327 reports.

Analysis of cases:

#### Blood and Lymphatic disorders

There were 132 events reported within this System Organ Class (SOC).

The most frequently reported events are tabled

Adverse event	No of reports
Thrombocytopenia	27
Anemia	24
Leukopenia	21
Bone Marrow Depression	15
Febrile neutropenia	13
Neutropenia	13
pancytopenia	11

Myelosuppression is a common complication of chemotherapeutic treatment of patients with cancer. This issue is sufficiently addressed in the SPC of carboplatin

#### Cardiac disorders

The most frequently reported adverse events are tabled

Adverse event	No of reports
Cardiac failure	4
Cardiac arrest	2
Cardiorespiratory arrest	2
Myocarditis	1
Palpitations	1
Tachycardia	1

According to the carboplatin SPC cardiovascular adverse events have occurred in 5% or fewer patients and death have occurred from cardiovascular events in less than 1% of patients. In total 11 adverse events in this SOC were reported.

#### **Congenital familial and genetic disorders**

There was 1 case of a patient with a retinoblastoma experienced progression of the disease

#### **Ear and Labyrinth disorders**

The most frequently reported events (in total 25) in this SOC concerned:

<b>Adverse event</b>	<b>No of reports</b>
Deafness	10
Ototoxicity	10
Hyperacusis	2

Clinically significant hearing loss in paediatric patients has been reported specifically when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

#### **Endocrine disorders**

There were 8 reports: 3 cases of hypothyroidism, 2 of hypo-aldosteronism 1 diabetes insipidus and 1 case of inappropriate ADH secretion

These cases were most likely due to concomitant medication and or the progression of the patients underlying disease.

#### **Eye Disorders**

Most of these reports are confounded by the underlying disease (retinoblastoma or another brain tumour)

#### **Gastrointestinal disorder**

Most frequently reported were vomiting and diarrhoea

#### **General disorders and administration site disorders:**

In this SOC there were 90 reports of adverse events, the most frequently reported being: death, pyrexia rigors and extravasation.

Patients that are treated with the drug have a high underlying mortality. Some of the fatal cases are due to immunosuppression and myelosuppression that may have led to severe infarction and bleeding.

The suppression of immunity and myelosuppression are well known adverse events of the therapy.

#### **Hepatobiliary disorders**

12 events were reported an a causal role of carboplatin cannot be ruled out

In the 6 reported cases 5 were also receiving concomitant medication that was known to be implicated in hepatic dysfunction and in 2 cases there were metastatic tumours in the liver due to the primary disease.

#### **Immune system disorders**

33 events were reported, the most frequently (27) concerned hypersensitivity. The occurrence of hypersensitivity is seen in approximately 2% of all patients receiving carboplatin.

In view of the total number of reports (327) the occurrence of hypersensitivity (27) seems higher than in the overall population.

#### **Infections and Infestations:**

This SOC involved in total 56 adverse events: sepsis (12), infection (9)

The occurrence of infections is a well-known adverse effect of carboplatin due to its effect on the blood cells

### **Injury poisoning and Procedural Complications**

8 events were reported. The events experienced as a result of overdose, accidental exposure and medication error included abdominal pain, anorexia, diarrhoea, increased liver function, tests, myelosuppression, nausea, nephritis, neutropenia, sepsis and vomiting.

### **Investigations**

There were 42 events mostly concerning liver enzymes increase.

### **Metabolism and Nutrition Disorders.**

The most frequently reported events concerned dehydration (10) anorexia (6) and sarcoidosis (3)

### **Musculoskeletal and Connective Tissue Disorders**

Events (6) reported included pain in extremity (2), back pain (1) Bone pain (1) osteoporosis (1) and rickets (1).

### **Neoplasma benign, malignant and unspecified**

41 events were reported, most frequently: leukaemia (6) neuroblastoma (5) acute myeloid leukaemia (3), myelodysplastic syndrome (3) and treatment related secondary malignancy (3).

Treatment related secondary malignancies are known to occur under multidrug regimen

Of the cases of leukaemia there were 4 leukaemias likely secondary to carboplatin and or other chemotherapeutic agents.

The majority of cases concerned the progression of underlying malignancies.

### **Nervous system disorders.**

In total 42 events were reported, convulsions (12) the most frequently.

### **Psychiatric events**

In total 9 events were reported, agitation (2) anxiety (2) confusion (1)

No clear pattern or signal emerged from these data.

### **Renal and Urinary disorders**

In total 38 events, most frequently cystitis (5), acute renal failure (4)

### **Reproductive System and Breast Disorders**

Two events were reported.

### **Respiratory thoracic and Mediastinal Disorders**

In this SOC were 41 events reported, cough dyspnoea respiratory distress

### **Skin and subcutaneous tissue disorders**

There were 70 events reported in this SOC, the most frequently were as expected: urticaria (18), rash (16), pruritus (12) erythema (8).

Most appear to be parts of an allergic reaction.

### **Surgical and Medical Procedures**

There were 4 events reported within this SOC

### **Vascular disorders**

12 events were reported the most frequent; and flushing (5), haemorrhage (2)

### **Fatal cases**

Death was reported most frequently (30 times) under the System Organ Class general Disorders Administration Site Disorders. In total there were 123 cases with fatal outcome. Many of the fatalities are probably due to progression of underlying disease. In addition there are also some fatal cases due to immunosuppression and myelosuppression that may have led to severe infection and bleeding, which is in line with the known risk/benefit profile of carboplatin.

### **Summary of the findings**

A review of all reported adverse events did not indicate new information concerning the safety profile of carboplatin. There is no clearly different pattern in children as compared to the total population in the reported adverse events.

The most frequently involved SOC was as expected Blood and Lymphatic Disorders, followed by General disorders and Administration Site Conditions Gastro intestinal Disorders and Skin and subcutaneous Tissue Disorders

<b>SOC</b>	<b>Total no of events</b>	<b>Most frequently reported event</b>
Blood and Lymphatic Disorders	132	Myelosuppression
General disorders and Administration Site Conditions	90	Dehydration and pyrexia
Gastro intestinal Disorders	80	Diarrhoea and vomiting

From a safety perspective the adverse events observed were consistent with those previously observed and described in the carboplatin label.

The paediatric population does not seem to differ in the occurrence and the severity of the adverse events from the overall population. The adverse event hypersensitivity (Immune system disorders) is seen in approximately 2% of all patients receiving carboplatin. In the data provided the occurrence of hypersensitivity (27) seems higher than in the overall population.

Overall the information provided supports the known safety profile.

#### **Assessor's comment:**

*The adverse events and additional safety data from the studies are consistent with the known safety profile for the two products in use in adults. As could be expected given the known adverse events (AEs) associated with carboplatin and irinotecan, hematologic toxicity including anemia, thrombocytopenia, or neutropenia was observed. Diarrhea and other gastrointestinal toxicities are labelled side effects of irinotecan. Adverse events previously associated with carboplatin included nausea, vomiting and neuropathy. No SPC changes are warranted. As discussed above, the limited number of patients in each treatment group makes it difficult to draw any conclusions regarding comparisons between the groups.*

### III. SUMMARY AND OVERALL CONCLUSION

The literature gives evidence of a broad use of carboplatin in a range of children malignancies including both CNS and non-CNS solid tumours. It appears that in children with malignancies, carboplatin is an effective anti-tumour agent in the treatment of several paediatric malignancies. Neuroblastoma, gliomas, retinoblastoma and Wilm's tumour represent the tumour types for which treatment carboplatin is most commonly used in combination chemotherapy induction regimens, high-dose consolidation regimens and combined-modality regimens (in particular, with radiation therapy and/or bone marrow transplantation). It appears that, due to reduced toxicity profile, carboplatin is more commonly used than its parent compound, cisplatin.

The two submitted BMS studies were specifically designed with the US FDA to provide information regarding the safety and efficacy of carboplatin in the paediatric population.

It was hoped that the data generated by these trials might result in dosage recommendations for this group of patients. Unfortunately, neither the pharmacokinetic nor the clinical results can support the establishment of a safe and active dose of carboplatin in this population and with the particular combination regimen studied.

The applicant argued that a posology recommendation for children cannot be given, as data from pharmacokinetic Study CA124001 are not reliable. Further, the literature shows that there is a large between patient variability in carboplatin AUC especially in the paediatric population (three- to fourfold difference). If a reliable measure of renal function is available for a patient, particularly if renal impairment is suspected, the use of dosing formula appears to offer an advantage over dosing based on surface area alone. This could be mentioned in section 5.2 of the SPC.

The Applicant is not seeking an indication for carboplatin in paediatric populations, nor does it support the addition in the prescribing information of any dosage recommendation or any specific description of the safety and efficacy of these studies, opinion shared by some Member States. Of note, the US Prescribing Information does not include any information from these studies ("FDA does not recommend addition of any information based on the paediatric studies conducted to the label", as included in the reviewer's assessment).

The Applicant acknowledges the differences in the information included in current SPC regarding paediatric wording across Europe, and would suggest, as already included in the majority of the local SPCs, to include the following information:

#### 4.2 Posology

Paediatric patients: there is insufficient information to support a dosage recommendation in the paediatric population.

#### 5.1 Pharmacodynamics properties

Paediatric patients: safety and efficacy in children have not been established.

The Applicant would recommend this wording be implemented across Europe.

**Rapporteurs' comments and conclusion:**

The Rapporteurs agree with the MAH that, today, there is no descriptive information on paediatric use of carboplatin. The SPC can only state the insufficiency and limitations of the data, and would thus be of limited use to prescribing oncologists. Nevertheless, the variability of carboplatin pharmacokinetics could be mentioned in the SPC section 5.2.

The following text is proposed:

*“Carboplatin clearance has been reported to vary by 3- to 4- fold in paediatric patients. As for adult patients, literature data suggest that renal function may contribute to the variation in carboplatin clearance.”*

## IV. PROPOSED CHANGES IN THE SPC

Paediatric data of Pharmacokinetics Study CA124001 of AUC of carboplatin as measured platinum in plasma ultra filtrate are considered of no clinical value, as inadequate sample processing at the clinical sites may have taken place.

An integrated overview of published reports of paediatric trials where carboplatin was used has been given by the MAH. It shows that carboplatin is used in a range of children malignancies including both CNS and non-CNS solid tumours, but it could not provide an acceptable posology recommendation for children for carboplatin. The literature shows that there is a large between patient variability in carboplatin AUC.

Rapporteurs consider the Applicant acknowledgement of lack of data to give a posology recommendation for children acceptable. The MAH does not seek an indication for the paediatric population.

The Applicant acknowledges the differences in the information included in current SPC regarding paediatric wording across Europe, and would suggest, as already included in the majority of the local SPCs, to include the following information:

### 4.2 Posology

Paediatric patients: there is insufficient information to support a dosage recommendation in the paediatric population.

### 5.1 Pharmacodynamics properties

Paediatric patients: safety and efficacy in children have not been established.

The Rapporteurs endorse the Applicant's recommendation that this wording be implemented across Europe.

Rapporteurs agree with the MAH that, today, there is no conclusive information on paediatric use of carboplatin and any of these data in the SPC would thus be of limited use to prescribing oncologists. The SPC can only state the insufficiency and limitations of the data. Nevertheless, the variability of carboplatin pharmacokinetics could be mentioned in the SPC section 5.2.  
The following text is proposed:

“Carboplatin clearance has been reported to vary by 3- to 4- fold in paediatric patients. As for adult patients, literature data suggest that renal function may contribute to the variation in carboplatin clearance.”