CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Paclitaxel Accord 6 mg/ml, concentrate for solution for intravenous infusion Accord Healthcare B.V., the Netherlands

paclitaxel

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1444/001/DC
Registration number in the Netherlands: RVG 102965

Date of first publication: 6 September 2010
Last revision: 3 October 2011

Pharmacotherapeutic group:	plant alkaloids and other natural products, taxanes
ATC code:	L01CD01
Route of administration:	intravenous
Therapeutic indication:	ovarian carcinoma (first-line, second-line chemotherapy); breast carcinoma (adjuvant/single agent treatment); advanced non-small cell lung carcinoma (in combination with cisplatin); AIDS-related Kaposi's sarcoma (limited efficacy data) - see next page for more information on the approved indications.
Prescription status:	prescription only
Date of authorisation in NL:	31 August 2010
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, LT, LV, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Paclitaxel Accord 6 mg/ml, concentrate for solution for intravenous infusion from Accord Healthcare B.V. The date of authorisation was on 31 August 2010 in the Netherlands.

The product is indicated for:

- Ovarian carcinoma
  In the first-line chemotherapy of ovarian cancer for patients with advanced carcinoma of the ovary or with residual disease (>1 cm) after initial laparotomy, in combination with cisplatin.
  In the second-line chemotherapy of ovarian cancer for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum-containing therapy.

- Breast carcinoma
  In the adjuvant setting, paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.
  Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable (see sections 4.4 and 5.1).
  As a single agent, paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have either failed or are not candidates for standard, anthracycline-containing therapy.

- Advanced non-small cell lung carcinoma
  Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

- AIDS-related Kaposi's sarcoma
  Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy.
  Limited efficacy data supports this indication; a summary of the relevant studies is shown in section 5.1 of the approved SPC.

A comprehensive description of the indications and posology is given in the SPC.

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Taxol 6 mg/ml concentrate for solution for infusion which has been registered in the UK by Bristol Myers Squibb since December 1992. In the Netherlands, Taxol 6 mg/ml (NL License RVG 16265) has been registered since 20 September 1993. In addition, reference is made to Taxol authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised

medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Paclitaxel Accord 6 mg/ml, concentrate for solution for infusion is a product for parenteral use in non-aqueous solution, and has the same quantitative composition as the reference product, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is paclitaxel, isolated from natural sources. Paclitaxel is an established active substance, described in the European Pharmacopoeia and the Pharmacopoeia of the United States (Ph.Eur., USP*). It is a white or almost white crystalline powder, practically insoluble in water, soluble in methanol and freely soluble in dichloromethane. The α-form is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Paclitaxel is manufactured by extraction from dried parts of *Taxus canadensis* followed by successive extraction, purification and crystallization steps. Detailed information about the manufacturing process and validation has been provided. The starting material crude paclitaxel has been adequately characterized and complies with the Ph.Eur. monograph on Pesticides Residues.
The solvents used during manufacture of the starting material and active substance are listed, and adequate specifications are adopted. The drug substance has been adequately characterized.

Quality control of drug substance
The active substance specification includes tests for appearance, identification, specific optical rotation, related substances, assay, water content, heavy metals, residual solvents, microbial purity and bacterial endotoxins. The specifications for the drug substance paclitaxel are based on the Ph.Eur. monograph for paclitaxel, sourced from natural sources. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The available stability data are not generated in accordance with ICH requirements and current specifications/Ph.Eur. monograph. It is therefore specified that the active substance batches comply with the pharmacopoeial monograph immediately prior to manufacture of the finished product.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA.*

Medicinal Product

Composition
Paclitaxel Accord 6 mg/ml is a clear colourless to slightly yellow non-aqueous solution with a pH in range of 3.0-5.5 and an osmolarity of > 4000 mOsm/l.

The concentrate for solution for intravenous infusion is packed in type I glass vials (closed with bromobutyl omniflex plus rubber stopper) containing 30 mg, 100 mg or 300 mg of paclitaxel in 5 ml, 16.7 ml or 50 ml of solution respectively.

The excipients are: anhydrous ethanol, polyoxyl castor oil (macrogolglycerol ricinoleate).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions are explained. The formulation was based on similarity with the reference medicinal product Taxol 6mg/mL. Development studies are performed to determine the photodegradation, pH and surface tension of paclitaxel solution for injection. The drug product has the same pharmaceutical form and quantitative composition as Taxol 6 mg/mL, as well as a comparable profile with respect to appearance, pH, assay, related substances, water content and assay of alcohol. A comparison between the quantitative compositions was provided. The reference and proposed product are essentially similar. Since the product is a generic product for parenteral use it is exempted from bioequivalence studies.
The pharmaceutical development has been sufficiently described.

Manufacturing process
Paclitaxel is dissolved in the two media, after which the solution is filtered aseptically into the vials. The manufacturing process is a standard process for parenteral preparations for which heat treatment is not possible. The process has been adequately described. The process validation data from four production-scale batches of 50 ml, 16.7 and 5 ml filling volume demonstrate that the process is reproducible and provides a finished product that complies with the finished product specifications.

Microbiological attributes
Container closure integrity is established by dye ingress test method and microbial immersion method. Bacterial endotoxin content and sterility of the finished product are controlled and tested in accordance with the Ph.Eur.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The specification for the finished product at release and shelf life includes tests for appearance, identification, related substances, assay, water content, pH, alcohol content, extractable volume, particulate matter, sterility and bacterial endotoxins. All tests included in the specification have been satisfactorily described and validated. The specifications are mainly based on the USP monograph on paclitaxel injections and the Ph.Eur. monograph for parenteral preparations. Batch analyses results have been provided for four full-scale production batches. The results are in compliance with the requirements of the specification.

Stability of drug product
Stability studies have been performed on four full-scale production batches of the finished product, one batch per fill volume and an additional batch for the 50.0 ml volume. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in type I glass ampoules, upright and inverted. Results are available for 24 months long term, 12 months intermediate and 6 months accelerated storage conditions. When stored under accelerated conditions, 2 out of specifications results

are observed. An increase in impurities is less pronounced during storage at long term and intermediate conditions. Photostability studies show sensitivity of the product to light. Based on the stability data a shelf-life of 18 months could be granted, when stored in type I clear glass ampoules of 5 ml, 16.7 ml or 50 ml. The product should be stored below 25°C and kept in the outer carton in order to protect from light.

Compatibility/In-use stability

Compatibility and in-use stability testing has been performed. Samples were stored in non-PVC containers at 2-8°C and 23-17°C in concentrations of 0.3mg/ml and 1.2 mg/ml. The dilution studies have been performed with the following diluents:

- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 5% Dextrose in Ringer's Injection

No significant variation after storage and dilution has been observed. The claimed compatibility with reconstitution solutions has been adequately demonstrated and is identical to the innovator's claim.

In use stability was carried out on paclitaxel 6mg/mL. The product solution was withdrawn by sterile plastic syringe/needle followed by push back of the solution into the vials, once daily for 28 consecutive days. The results demonstrate that the product remains chemically, physically and microbiogically stable for 28 days at 25°C following multiple needle entries and product withdrawals. The claimed in-use stability as stated in the SPC is therefore justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Taxol 6 mg/ml concentrate for solution for infusion, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of paclitaxel released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Paclitaxel is a well-known active substance with established efficacy and tolerability.

Paclitaxel Accord 6 mg/ml, concentrate for solution for infusion is a parenteral non aqueous formulation. The member states consider the present application of this generic substance paclitaxel, as a concentrate for solution for infusion, approvable based on the comparability with prior approved registered generics (as well as with the innovator). The quantitative composition of Paclitaxel Accord 6 mg/ml is entirely the same as the originator. According to the guideline a bioequivalence study is not required when both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance (NfG CPMP/EWP/QWP 1401/98). Therefore, a bioequivalence study is not required. Paclitaxel Accord can be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan

Paclitaxel was first approved in 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of paclitaxel can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Taxol.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. Participants were asked to read the PL and asked for their first impression, followed by a diagnostic test of 12 questions and assessment of lay-out and content.

The results indicate that the information most relevant to the patients can be found (100%) and understood (98.8%). No recommendations were proposed to the structure and presentation of the PIL. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paclitaxel Accord 6 mg/ml, concentrate for solution for intravenous infusion has a proven chemical-pharmaceutical quality and is a generic form of Taxol 6 mg/ml. Taxol is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use and have the same quantitative composition in active substance and excipients, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other paclitaxel containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paclitaxel Accord 6 mg/ml, concentrate for solution for intravenous infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 11 March 2010. Paclitaxel Accord 6 mg/ml was authorised in the Netherlands on 31 August 2010.

A European harmonised birth date has been allocated (29 December 1992) and subsequently the first data lock point for paclitaxel is December 2012. The first PSUR will cover the period from March 2010 to December 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 August 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to perform process validation on the first three commercial batches of each of the 5 mL and 16.7 mL fill volume as per the validation protocol.

List of abbreviations

AC	Anthracycline and Cyclophosphamide
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
KS	Kaposi's Sarcoma
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NSCLC	Non-Small Cell Lung Carcinoma
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Submission of a new or updated Ph. Eur. certificate of suitability. New certificate from a new manufacturer (replacement or addition).	NL/H/1444/ 001/IA/001	IA	2-12-2010	3-1-2011	Approval	N
Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient).	NL/H/1444/ 001/IA/002	IA	4-8-2011	5-9-2011	Approval	N