ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTES OF ADMINISTRATION, APPLICANTS IN THE MEMBER STATES

Member State EU/EEA	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Austria		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin „Pharmachemie“ 15000 I.E. - Pulver zur Herstellung einer Injektionslösung	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Local injection	15 U (USP)/vial
Belgium		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	BLEOMYCINE TEVA 15U poeder voor oplossing voor injectie	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Bulgaria		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycine Teva 15U, прах за инжекционен разтвор	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Czech Republic		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin-Teva 15U, prášek pro přípravu injekčního roztoku	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Denmark		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin “Teva”	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Estonia		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin Teva	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
France		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycine TEVA 15 000 UI, poudre pour solution injectable	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Germany		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleo-TEVA 15 mg Pulver zur Herstellung einer Injektionslösung	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Intravenous administration Intra-pleural injection	15 U (USP)/vial
Italy		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomicina TEVA, 15 U polvere per soluzione iniettabile	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Latvia		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin Teva	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration	15 U (USP)/vial

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
						Local/Intratumoral injections	
Lithuania		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin Teva	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Luxembourg		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	BLEOMYCINE TEVA 15U poudre pour solution injectable	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Local/Intratumoral injections	15 U (USP)/vial
Netherlands		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycine 15 U (USP), poeder voor oplossing voor injectie	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Norway		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin Teva, Pulver og væske til injeksjonsvæske, oppløsning	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Poland		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin Teva	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection	15 U (USP)/vial

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
						Intraperitoneal administration Local/Intratumoral injections	
Portugal		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomicina Teva	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Slovak Republic		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomycin-Teva prášok na injekčný roztok	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Slovenia		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomicin Teva 15 U (USP), prašek za raztopino za injiciranje	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial
Spain		Pharmachemie B.V. Swensweg 5 P.O. Box 552 2003 RN Haarlem, The Netherlands	Bleomicina Teva 15 UI polvo para solución inyectable EFG	15 U (USP)/vial	powder for solution for injection	Intramuscular injection Subcutaneous injection Intravenous administration Intra-arterial administration Intra-pleural injection Intraperitoneal administration Local/Intratumoral injections	15 U (USP)/vial

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BLEOMYCIN PHARMACHEMIE AND ASSOCIATED NAMES (SEE ANNEX I)

Bleomycin belongs to the cytostatic antibiotics: it is a mixture of structurally related, alkaline, water soluble, glycopeptide antibiotics with a cytostatic effect. The effect of bleomycin rests on intercalation with single and double strands of DNA, resulting in single and double strand ruptures, which inhibit cell division, growth and DNA synthesis. In a lower degree bleomycin also affects the RNA and protein synthesis. The administration of bleomycin almost always takes place in combination with other cytostatic drugs and/or radiation therapy. In the Netherlands bleomycin is currently approved for the following indications:

- *Squamous cell carcinoma of Head and neck (SCCHN)*
- *Squamous cell carcinoma of external genitalia: penile carcinoma, cervix carcinoma.*
- *(Non-)Hodgkin´s lymphoma and other malignant lymphomas*
- *Testis carcinoma*
- *Intrapleural therapy of malignant pleural effusion.*

The Application for Bleomycin Pharmachemie was submitted as a generic application based on the marketing authorisation granted for the reference product in the Netherlands on 18 November 1997. Concerns were raised on the proposed indications by an objecting member state, Germany. Because the benefit/risk assessment for these indications was negative for the originator product and because the indications were consequently deleted from the authorised indications for all bleomycin-containing products in Germany, the indications were regarded as new indications, and the objecting member state considered that the submitted data was insufficient for granting a marketing authorisation for the proposed new indications. Although the applicant was willing to remove the indications objected to by the objecting CMS, the RMS and the other positive CMSs were in favour of retaining these indications. Because consensus could not be reached, the CMD(h) referred the procedure to the CHMP. The CHMP assessed the available data in order to establish whether the two indications can be supported.

The CHMP noted that bleomycin is in clinical use since the 1960ies, thereby explaining the lack of a clinical development programme. Most of the presented data describe bleomycin as component of multi-drug chemotherapy including cisplatin and therefore the individual contribution of bleomycin cannot be unequivocally determined, however a number of studies and publications clearly indicate that bleomycin demonstrates efficacy.

Regarding the indication in Head and Neck cancer, the CHMP is of the opinion that although bleomycin has obvious disadvantages related to its toxicity (pulmonitis, pulmonary fibrosis, stomatitis and skin changes), there is still a role for bleomycin in (neoadjuvant) treatment of the disease. In addition to the documentation already provided during the decentralised procedure, supporting a modest but certain role for bleomycin in the treatment of SCCHN, a number of recent reports support the role of bleomycin in conjunction with other chemotherapeutic moieties, identifying both a recovery ratio (RR) of 34% in second line treatment and the improvement of loco-regional control and survival in patients with advanced HNC through concomitant postoperative radio- and chemotherapeutical treatment with mitomycin C and bleomycin. Although bleomycin is currently not regarded as an essential component in the first line systemic treatment of SCCHN, it still constitutes a treatment option for (concomitant) chemotherapy, or in conjunction with RT, and can therefore not be considered obsolete for this indication. The CHMP therefore considered the indication to be acceptable.

Regarding the indication in Epidermoid carcinoma of external genitalia, the CHMP noted that bleomycin is currently still in use in cervical cancer, and it was agreed that although the clinical efficacy is modest in

this indication, as well as in penile cancer, several recent trials have illustrated the significance of bleomycin in these indications. The combination of bleomycin, vindesine, mitomycin C and cisplatin in patients with recurrent and/or metastatic squamous cell carcinoma of the cervix was recently shown to be of benefit with regards to survival and a phase II study showed bleomycin to be part of a clinically relevant alternative treatment regimen for cisplatin, in patients with recurrent cervical cancer. Although response rates are in general higher with bleomycin containing regimens, the added toxicity is readily acknowledged. Furthermore the difficulty to assess the sole efficacy of bleomycin when results are obtained with combination regimens is recognized, however the overall favourable efficacy of bleomycin containing regimen supports the indication for bleomycin.

The CHMP considered that although bleomycin is not an obvious first line component for systemic treatment of cervical cancer, bleomycin remains a useful cytostatic drug that has to remain available to patients for this indication. The same is applicable for the indication penile cancer; the indication is supported by reports suggesting a modest efficacy for this disease. Therefore, despite overt toxicity and modest efficacy, the CHMP considered that bleomycin is a valuable treatment option for systemic treatment, if deemed necessary for these indications. In the combination therapy bleomycin is also of value, even though the evidence of the sole contribution of bleomycin is not assessable.

The CHMP also noted that bleomycin is still in use and also mentioned in current treatment guidelines in Europe and North America, such as the SCCHN: Practice Guidelines in Oncology-v.2.2008 (HCCN, USA), the CCO (Cancer Care Ontario) Formulary, revised 2006/2007, and the Guidelines on penile cancer (March 2004) of the European Association of Urology.

In conclusion, the CHMP considered that this efficacy outweighs the toxicity of the product, and that the benefit/risk balance is positive. Therefore the CHMP is of the opinion that bleomycin is still a valuable chemotherapeutic drug, and adopted the totality of the proposed indications, for Bleomycin Pharmachemie:

Bleomycin is intended for the treatment of:

- *Squamous cell carcinoma (SCC) of the head and neck, external genitalia and cervix.*
- *Hodgkin's lymphoma.*
- *Non-Hodgkin's lymphoma of intermediate and high malignancy in adults.*
- *Testis carcinoma (seminoma and non-seminoma).*
- *Intrapleural therapy of malignant pleural effusion.*

GROUNDS FOR OPINION

Whereas

- the observed toxicity risks are outweighed by the established efficacy of bleomycin,

- the efficacy of bleomycin can be considered as established through published literature and current treatment guidelines in Europe and North America

- and taking into account the current therapeutic use of bleomycin,

the CHMP has recommended the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination Group procedure as mentioned in Annex III for Bleomycin Pharmachemie and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.