CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Dysport 300 E, powder for solution for injection IPSEN Farmaceutica B.V., the Netherlands

Clostridium botulinum type A toxin-haemagglutinin complex

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 110868

15 January 2014

Pharmacotherapeutic group:	other muscle relaxants, peripherally acting agents
ATC code:	M03AX01
Route of administration:	intramuscular
Therapeutic indication:	blepharospasm; hemifacial spasm; spasmodic torticollis; symptomatic treatment of hyperhidrosis of the axillae; arm spasticity after a stroke in adults
Prescription status:	prescription only
Date of authorisation in NL:	26 February 2013
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

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

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Dysport 300 E, powder for solution for injection from IPSEN Farmaceutica B.V. The date of authorisation was on 26 February 2013 in the Netherlands.

The product is indicated for

- Treatment of blepharospasm and hemifacial spasm
- Treatment of spasmodic torticollis
- Symptomatic treatment of hyperhidrosis of the axillae
- Arm spasticity after a stroke in adults.

The product should not be used in children under the age of 12 years.

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

Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca2+ which culminate in transmitter release. It does not affect postganglionic cholinergic transmission or postganglionic sympathetic transmission.
The action of toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly, there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally the toxin inhibits the release of acetylcholine by disrupting the Ca2+ mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis

This national procedure concerns a line extension to Dysport 500 E powder for solution for injection (NL License RVG 17505), which was authorised on 2 December 1993. The formulation for the 300 U/vial is the same as for the 500 U/vial, except that the drug product contains 60% of the amount of *C. botulinum* toxin type A. The objective of this extension application for a 300 U vial size is to allow treating physicians more flexibility and limit the disposal of unused toxin.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data.
The active substance of Dysport 300 powder for solution for injection is considered to be well-known. Reference is made to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the previous Dysport 500 U authorisation. This information is not fully available in the public domain. Authorisations for line extensions are therefore linked to the 'original' authorised medicinal product. This reference to the non-clinical and clinical studies performed with Dysport 500 E powder for solution for injection is acceptable for this line extension. Separate studies are not required.

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 line extension.

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 *Clostridium botulinum* type A toxin-haemagglutinin complex. The European Pharmacopoeia (Ph.Eur.*) includes a monograph on *Botulinum* toxin type for injection.

The quality dossier on the drug substance is largely in line with that approved for the 500 U/vial presentation, as the same substance is used. Various sections have however been updated. Drug substance specifications were revised based on results of a data review. This resulted in tightening of some of the release specifications. Also additional stability data have been provided, all of which meet the established specifications.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Dysport 300 E, powder for solution for injection contains per vial 300 E *Clostridium botulinum* type A toxin-haemagglutinin complex. It is a white lyophilised powder for injection. Prior to use the 300 U/vial is reconstituted with 0.6 or 1.5 mL of sodium chloride for injection (0.9% w/v) to yield a solution containing 500 or 200 Units/mL, respectively.

The powder is packed in 3 mL nominal capacity clear, neutral type I glass vial with an aluminium crimp seal with a polypropylene flip top seal.

The excipients are: albumin, lactose monohydrate.

Pharmaceutical development
Dysport 300 U/vial is very closely related to two existing approved medicinal drug products Dysport 500 U/vial and Azzalure 125 U/vial from the same MAH. The only difference between the products is the quantity of toxin present per vial. Experience gained with the manufacture and control the 500 and 125 U/vial has therefore been used as a basis for the development of the 300 U presentation.
The formulation of the drug product has not changed during the development of the proposed product. Initially the 300 U/vial batches presented were manufactured with a 5% overage of bulk active substance, which results in an extra 0.15 ng of active substance protein. Although future commercial batches of 300 U/vial product will not contain an overage, the data provided are considered supportive of the intended commercial process. The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The manufacturing process consists of preparation of bulk drug product solution, sterilisation by filtration, aseptic vial filling and lyophilisation of drug product. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 6 batches. Some parts of the validation are covered by data of the 500 U process, which is acceptable given the similarity in formulation (mainly lactose and human serum albumin) and production process.

Microbiological attributes

During the manufacture of the product bioburden testing is carried out prior to sterile filtration of the bulk formulated product and sterility testing is carried out at the end of the process as part of the finished product release testing. These microbiological controls are common for this type of sterile freeze-dried product and therefore acceptable.

Control of excipients
Dysport contains two pharmacopoeial excipients: human albumin solution (Ph. Eur./USP) and lactose monohydrate (Ph.Eur./USP-NF). In addition, water for injections (Ph.Eur./USP) is used to prepare the bulk formulation solution and is eliminated from the drug product during the freeze-drying process. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, reconstitution time, pH, uniformity of fill, mean fill volume expressed by weight, identity, moisture content, protein, lactose, potency (toxicity), endotoxin, sterility, abnormal toxicity and sub-visible particulates. The analytic methods have been sufficiently validated.
Batch analytical data on 4 batches have been provided, demonstrating compliance with the specification.

Compatibility
Prior to use Dysport 300 U is reconstituted with saline solution in the same way as used for the registered products Dysport 500 U/vial and Azzalure 125 U/vial, for which there are no compatibility issues. Since the only difference in the formulations is the quantity of drug substance, no compatibility issues are anticipated with the proposed product.

Stability of drug product
Stability data on the product have been provided for 4 batches in accordance with applicable European guidelines. The 300 U vials were stored under refrigerated storage conditions (2-8°C) for 24 months. All batches remain within the specifications under these conditions. Therefore a shelf life of 24 months when stored between 2°C and 8°C was granted.
Based on in-use stability results, the applicable shelf life for the reconstituted solution is 8 hours when stored at 2-8°C. Post approval this shelf life has been extended to 24 hours.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There is a minimal risk for the presence of adventitious viruses in the Human Albumin Solution Ph Eur. A specific EMA Plasma Master File certificate for the human albumin used has been issued. Lactose monohydrate is derived from bovine milk. The MAH stated that the likelihood of contaminating viruses in bovine milk is low and that the heat treatment stages provide adequate assurance that the lactose monohydrate, used as an excipient in the Dysport formulation, presents a minimal risk for the presence of adventitious viruses.

II.2 Non-clinical aspects

This product is a line extension to Dysport 500 E powder for solution for injection, which is available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the previous application. Therefore the application has not undergone additional preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The environmental risk assessment specified in EMEA/CHMP/SWP/4447/00, 'Guideline On The Environmental Risk Assessment of Medicinal Products For Human Use' has been applied. The phase I estimate of $PEC_{SURFACEWATER}$ value is below 0.01 µg/L, whatever the dose considered. No other environmental concerns are apparent for the active substance. It may therefore be assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

II.3 Clinical aspects

Clostridium botulinum type A toxin-haemagglutinin complex is a well-known active substance with established efficacy and tolerability.

The MAH did not conduct any new pharmacokinetic nor clinical efficacy/safety studies with the 300 U/vial presentation. To support the application, the MAH referred to pharmacokinetic and clinical efficacy/safety data from previously conducted studies with Dysport 500 E, powder for solution for injection. This is acceptable for this line extension, as the formulation for the 300 U/vial is the same as for the 500 U/vial, except that the drug product contains 60% of the amount of *C. botulinum* toxin type A.

Risk management plan
The MEB considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
As laid down in the Risk Management Plan, the MAH continues to monitor all adverse reaction reports which include events compatible with the mechanism of action of the toxin. Events potentially related to local or remote distribution of toxin effects have been identified as an important risk. The MAH describes additional risk minimisation activities such as educational material for patients/caregivers, health care professionals and internal MAH staff to increase awareness. PSURs will be submitted on a yearly basis.

Product information

SmPC
The content of the SmPC approved during the national procedure is in accordance with that accepted for Dysport 500 E, solution for injection.

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 a pilot test with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. After the pilot round, some revisions were made to the PL. In both test rounds the PL passed the criteria for a successful user test: more than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Dysport 300 E, powder for solution for injection has a proven chemical-pharmaceutical quality and is an approvable line extension to Dysport 500 E. Dysport powder for solution for injection is a well-known medicinal product with an established favourable efficacy and safety profile.

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

For this application the MAH refers to the studies conducted with Dysport 500 E. Separate non-clinical or clinical studies were not required.

The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, has therefore granted a marketing authorisation. marketing authorisation. Dysport 300 E, powder for solution for injection was authorised in the Netherlands on 26 February 2013.

Botulinum toxin A is part of the PSUR worksharing of the Heads of Medicines Agencies (HMA). PSURs have to be submitted on a yearly basis. The MAH will follow the schedule as mentioned on the HMA website for submission of the PSURs.

There were no post-approval commitments made during the procedure.

List of abbreviations

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
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
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
SmPC	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	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Replacement or addition of a site where batch control/testing takes place.	IB	13-6-2013	21-8-2013	Approval	N
Change in test procedure for the finished product.	IB	13-6-2013	1-8-2013	Approval	N
Introduction of new Working Seed Banks.	IB	13-6-2013	11-7-2013	Approval	N
Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certifícate of Suitability is part of the approved dossier	IB	13-6-2013	1-8-2013	Approval	N
Introduction of a Summary of Pharmacovigilance system.	IA/G	4-10-2013	14-10-2013	Approval	N
Extension of the shelf life of the finished product after reconstitution: from 8 to 24 hours when stored at 2-8°C.	IB	7-11-2013	10-12-2013	Approval	N