Method of administration

The exposed central portionof the rubber stoppershould be cleaned with alcohol immediatelyprior to piercing theseptum. A sterile 23 or25 gaugeneedle should be used.
When treating strabismus, Dysportis reconstituted with 1.0mlof sodium chloride injection B.P. (0.9) to yielda solution containing 500units per 1 mlof Dysport. An aliquot(0.5ml) of this solutionis then placed in 9.5mlof sodium contains 25units per 1 mlof Dysport. When the needle isin the best position,inject 0.1ml of Dysport. Keep the needle *in situ* for 45 seconds topromote diffusion of the Dysport into the musclerather than tracking backdown the path of the needle. A newsterile needle and syringeshould be used toenter the vial on eachoccasion for dilution orremoved of Dysport

Contra-indications
Dysport is contraindicated inpregnancy.

Special warnings and specialprecautions
For the treatment ofspasmodic torticollis and paediatriccerebral palsy and adult post-strokespasticity. Dysport shouldonly be injected by specialists experiencedin the diagnosis and management of this conditionand who have receivedtraining on the administration of Dysport. Carefulconsideration should be given before the reinjection ofpatients who have experienceda previous allergic reaction. The riskof a further allergicreaction must be considered in relation tothe benefit of treatment.
Dysport should only beused with caution underclosed supervision in patients with subclinicalor clinical evidence ofmarked defective neuromuscular transmission. Such patientsmay have an increased Sensitivity to agents suchas Dysport which mayresult in excessive muscle weakness.

Training: Ipsen will facilitate training in administration ofDysport injections. There are noreports of any immuneresponse after the local administration of *Clostridium botulinum* Type A toxin-haemagglutinin complex in accordancewith the doses recommended when treating blepharospasmand hemifacial Spasm. Antibody formation tobotulinum toxin has beennoted in a small number of torticollispatients and in onepaediatric cerebral palsy patient receiving therapywith Dysport. Clinically,this has been detected by substantialdeterioration in response totherapy or a need for consistentlyincreasing doses.
This product contains asmall amount of humanalbumin. The risk of transmission of viral infectioncannot be excluded withabsolute certainty following the useof human blood orblood products.

Interaction with other medicamentsand other forms of interaction
No interactions of clinicalsignificance have been reported.

Pregnancy and Lactation
Teratological andother reproductive studies havenot been performed with Dysport. Thesafety of its usein pregnant or lactating women has notbeen demonstrated.

Effects on ability todrive and use machines
None known.

Undesirable effects
Adult spasticity of thearm Post-Stroke
Muscle weakness is themost commonly reported adverseevent in clinical studies and inthe literature, for thispatient population. In the two pivotal studiesusing DYSPORT for armspasticity post-stroke, the most frequentadverse events were infection(8.2%), flu-syndrome (6.1%),dry mouth, myastheniapain, constipation, diarrhea, pharyngitis and somnolence(each with an incidenceof 4,1%). The majority ofevents resolved within 2weeks.
Dysphagia has been reportedat doses in excessof 2700 units given in one doseor when given asa divided dose 12weeks apart. No cases werereported in pivotal studies.

Paediatric cerebral palsy spasticity

Adverse event incidence hasbeen assessed by three prospective studies involving 142patients treated with Dysport, and 75 patients treatedwith placebo.
Adverse events with anincidence of ≥5% following Dysport treatment were leg pain(8%),pharyngitis (8%),accidental injury(7%), bronchitic%), and fever(6%),thosewith an incidence of 1-5% were viralinfection(5%),infection(4%,rhinitis(4%), convulsion(4%),upper respiratory tract infection(4%), asthenia(3%),asthma(3%),cough(3%),vomiting (3%),cold(2%),diarrhoea(2%), urinary incontinence (2%),abnormal gait(1%), gastroenteritis (1%),laryngitis (1%),and somnolence(1%).
The incidence of manyof these adverse events(pharyngitis, bronchitis,fever,viral,infection, rhinitis, upperrespiratory tract infection, cough,vomiting, cold)was similar in placebotreated patients,and probably indicates thetypical spectrum of illnessin a paediatric population. Also,the incidence of convulsionswas identical in placebo treatedpatient, and reflects oneof the most frequent concomitant problems associatedwith cerebral palsy.
The incidence of accidentalinjury(falls) demonstrated the biggest different with placebotreated patients(1%), and itis likely that these adverseevents are due toover-weakening of the target muscle and/orthe local spread ofDysport to other muscle involved in ambulationand balance. The reportsof abnormal gait may alsobe the result ofsuch an effect. Another local side effect wasleg pain; predominantly calfpain. Although this pain appears tobe distinct from anypain experienced from the injection itself, itwas reported for 5%ofplacebo treatments.
Asthenia and urinary incontinencewere associated with higher dose of Dysport (20-30units/kg),and may be theresult of systemic spread of toxin.

Spasmodic torticollis
Side effects may occurmainly from deep ormisplaced injections temporarily paralysing other nearbymuscle groups. The injections have been associatedwith a burning sensationwhich lasts for 1-2 minutesafter injection. In patientstreated for torticollis, dysphagia is themost frequently reported adverse event. In a double-blindplacebo controlled trial theincidence of dysphagia was 29% followingtreatment with 500 unitsof Dysport and 10% inthe placebo group. Thisappears to be dose related and occurs mostfrequently following injection intothe sternomastoid muscle. A softdiet may be requireduntil symptoms resolve. In thosepatients severely affected, laryngoscopy has identified poolingof saliva.
Aspiration may occur rarelyand be of potentialconcern in those patients with pre-existing respiratoryproblems. Less frequently reported events include weaknessof the neck muscles,dryness of mouth and voicechanges. A more generalisedweakness and visual disturbances (including diplopiaand blurred vision) have occasionally been reported. Respiratorydifficulties have been noted on rare occasionsin association with highdoses.
These side effects maybe expected to resolvewithin two to four weeks. Allergic reactions suchas skin rashes andinfluenza-like symptoms have occasionally beennoted.

Blepharospasm and hemifacial spasm
Side effects may occurfrom deep or misplacedinjections of Dysport, temporarily paralysing othernearby muscle groups. They may also occurfrom exacerbation of pre-existingeyelid abnormalities or from aninitial over-correction. Ptosis isthe most common unwanted effect.
A few patients mayalso experience diplopia orsymptoms from spread of the paralyticeffect to mid-facial muscles.
These side effects maybe expected to resolvewithin two to four weeks. Keratitis and dryeyes due to reducedblinking have also been reported for whichthe use of artificialtears could be considered. Minor bruising andlid swelling may occurbut are short lived. Reversible externalophthalmoplegia has been reported after excessive dosing.
The injections have beenassociated with a burningsensation which lasts for 1-2minutes after injection. Allergicreactions such as skin rashesand influenza-like symptoms have occasionally been noted.

Overdose
Excessive doses may producedistant and profound neuromuscular paralysis. Respiratory supportmay be required where excessive doses causeparalysis of respiratory muscles. There is no specificantidote; antitoxin should notbe expected to be beneficial and generalsupportive care is advised.

Pharmacological Properties
Pharmacodynamic properties
Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmissionat the neuromuscular junction by a presynapticaction at a siteproximal to the release of acetylcholine. The toxinacts within the nerveending to antagonise those events thatare triggered by Ca^{2+} which culminate in transmitter release.It does not affect postganglionic cholinergic. transmission orpostganglionic sympathetic transmission. The actionof toxin involves aninitial binding step whereby thetoxin attaches rapidly andavidly to the presynaptic nerve membrance. Secondly there is an internalisation step in whichtoxin crosses the presynaptic membrane, without causing onsetof paralysis. Finally thetoxin inhibits the release ofacetylcholine by disrupting the Ca^{2+} mediated acetylcholine release mechanism,thereby diminishing the endplate potentialand causing paralysis.
Recovery of impulse transmissionoccurs gradually as new nerve terminals sprout andcontact is made withthe post synaptic motor endplate, aprocess which takes 6-8weeks in the experimental animal.

Pharmacokinetic properties
Pharmacokinetic studies with botulinumtoxin pose problems in animals because of thehigh potency, theminute doses involved, the large molecular weightof the compound andthe difficulty of labeling toxin to producesufficiently high specific activity.
Studies using I^{125} labelled toxin have shownthat the receptor binding is specific andsaturable, and the highdensity of toxin receptors is a contributoryfactor to the highpotency. Dose and time responses in monkeysshowed that at lowdoses there was a delay of 2-3days with peak effectseen 5-6 days afterinjection. The duration of action,measured by changes ofocular alignment and muscle paralysisvaried between 2 weeks and 8 months. Thispattern is also seenin man, and isattributed to the process ofbinding, internalisation and changesat the neuromuscular junction.

Pharmaceutical Particulars
List of excipients
Albumin and Lactose.

Incompatibilities
None known.

Shelf life
Do not exceed theexpiry date clearly indicatedon the outer box. The product maystored for up to8 hours at 2-8° C following reconstitution provided reconstitutionhas taken place in controlled and asepticconditions. Since the productdoes not contain an anti-microbial agent,from a microbiological pointof view, it isrecommended that the productshould be used immediately following reconstitution.

Special precautions for storage
Unopened vials must bemaintained at temperatures between 2° C and 8° C. Dysport must bestored in a refrigeratorat the hospital where the injectionsare to be carriedout and should not be given to thepatient to store. ReconstitutedDysport may be stored in a refrigerator(2° C -8° C) for up to8 hours prior touse, provided reconstitution has takenplace in controlled andaseptic conditions. Dysport should notbe frozen.

Nature and contents ofcontainer
Nature of container/closure :
Type 1 glassvials 3 ml capacity. 13mm chlorbutyl freeze-drying closures overseal by 13mm aluminum overseals withcentre hold, crimped over.

Contents of container :
A white lyophilised powderfor reconstitution.

Instruction for use/handling
Immediately after treatment ofthe patient, any residualDysport which may be presentin either vial orsyringe should be inactivated with dilute hypochloritesolution (1% available chlorine). Thereafter, allitems should be disposedof in accordance with standard hospitalpractice.
Spillage of Dysport shouldbe wiped up withan absorbent cloth soaked in dilute hypochloritesolution.

Name and Addressof the Holder ofthe marketing Authorisation
Ipsen Limited
190 Bath Road, Slough,Berkshiro, SL 13 XE.

Marketing Authorisation Number
PL 6958/0005

Date of Approval/Revisionof SPC
February 2001

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