

**Rapporteur's
Final Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

BACLOFEN

LIORESAL

UK/W/005/pdWS/001

Rapporteur:	UK – Shirley Norton
Date of the Final report (Day 120):	12 May 2010
Date of finalisation of PAR :	10 January 2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	LIORESAL
INN (or common name) of the active substance(s):	Baclofen
MAH:	See section VIII
Currently approved Indication(s)	Treatment of spasticity of the skeletal muscles due to various conditions
Pharmaco-therapeutic group (ATC Code):	Skeletal muscle relaxants
Pharmaceutical form(s) and strength(s):	Intrathecal Injection 50mcg/1ml, Infusion 10mg/20ml or Infusion 10mg/5ml Oral solution 5mg/5ml Tablets 10mg

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EXECUTIVE SUMMARY

Baclofen, an analogue of gamma-aminobutyric acid (GABA), is a centrally acting skeletal muscle relaxant. It interferes with the release of excitatory neurotransmitters (glutamate and aspartate) and inhibits monosynaptic and polysynaptic transmission at the spinal cord level. It may also act at supraspinal sites producing CNS depression. Baclofen is one of the drugs commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of neurological conditions. Patient selection is important when initiating therapy; it is likely to be of most benefit in patients whose spasticity severely affects daily activities and physiotherapy.

The data package submitted by the MAH under article 45 of the Paediatric Regulation in February 2009 comprised 2 preclinical reproductive animal studies, 1 clinical PK study in children receiving intrathecal infusion and 7 safety and efficacy clinical studies conducted in children and adolescents, together with a nonclinical and clinical overview report. All of these studies have been performed by the MAH. The MAH also conducted a literature search for publications relevant to paediatric population and included 8 published articles as supporting data. Based on the evidence submitted the MAH's view was that no change is necessary as a consequence of the data presented.

Based on the review of the presented paediatric data in the day 89 preliminary PdAR the rapporteur concluded the data from the submitted studies did not specifically indicate any need of major change the current paediatric information in the SmPCs. However, the precise wording of all European national SmPCs was not provided by the MAH, and in the review provided by the MAH, it is unclear whether all European countries where baclofen is approved do have similar recommendations for the indications and the dosage in paediatric patients. Therefore it was recommended that the MAH should review the national SmPCs as well as other available data in order to propose harmonised SmPC/PIL text regarding paediatric indications and dosage recommendations. Additionally the use of intrathecal administration of Baclofen in the paediatric population should be further reviewed to clarify all available information regarding dosing protocols, safety and effectiveness in different conditions.

The response from the MAH was received in December 2009 and included the MAH's response to the comments raised in the Preliminary Paediatric Assessment Report and by the CMS, study reports from 11 MAH sponsored studies of intrathecal Baclofen (ITB) in paediatric patients with severe spasticity of cerebral origin and the MAH's proposed changes to the SmPC/PIL. After the completion of the assessment of the new evidence, the draft final PdRA was circulated in April 2010 with the rapporteur's recommendations for the SmPC/PIL and comments were received from CMSs, which were included in the final Day 120 PdAR.

In June 2010 after the circulation of Day 120 assessment report, the MAH identified issues associated the proposed wording recommendations for both the oral liquid formulation of Baclofen and the ITB. Following discussions with the rapporteur, in July 2010 the MAH submitted further information on the dosing regimes for oral and intrathecal Baclofen. The rapporteur was of the view that this additional information should be reviewed prior the completion of the changes to the SmPCs /PILs of all Baclofen containing products; in December 2010 a supplementary assessment report was circulated and the comments of the CMSs were requested to better reflect the European practises of the use of Baclofen. The overall conclusions of the Rapporteur regarding the finalized wording included in the SmPCs and PIL of all products containing Baclofen across the EU were fully endorsed by CMSs.

RECOMMENDATION

Based on the review of the presented paediatric data the rapporteur considers that for all products containing Baclofen across the EU, it is recommended that SmPCs and PILs contain the following statements:

Proposed SmPC wording for Baclofen 5 mg, 10 mg and 25 mg tablets, 1 mg/mL syrup

Section 4.1 Therapeutic indications

Paediatric population

Baclofen is indicated in patients 0 to <18 years for the symptomatic treatment of spasticity of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

Baclofen is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

Section 4.2 Posology and method of administration

Paediatric population (0 to <18 years)

Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), in 2-4 divided doses (preferably in 4 divided doses).

The dosage should be raised cautiously, at about 1 week intervals, until it becomes sufficient for the child's individual requirements. The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

Baclofen tablets are not suitable for use in children below 33 kg body weight.

Section 4.4 Special Warnings and Precautions for use

There is very limited clinical data on the use of Baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.

Proposed PIL wording for Baclofen 5 mg, 10 mg and 25 mg tablets, 1 mg/mL syrup

Please read this product information carefully before you or your child is given Baclofen since it contains important information

1. What Baclofen is and what it is used for

Your doctor has decided that you or your child needs this medicine to help treat your condition.

Baclofen is used to reduce and relieve the excessive tension in your muscles (spasms) occurring in various illnesses such as cerebral palsy, multiple sclerosis, cerebrovascular accidents, spinal cord diseases and other nervous system disorders.

2. Before you take Baclofen

Children and adolescents:

Baclofen tablets are not suitable for use in children under 33 kg body weight.

3. How to take Baclofen

Use in children (0 to <18 years)

Children's treatment is adjusted to their body weight. Children's treatment is usually starts with very low dose (approximately 0.3 mg/kg/day), in 2-4 divided doses (preferably in 4 doses). The dosage then gradually increased until it becomes sufficient for the child's individual requirements, this may be between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given. Baclofen tablets are not suitable for use in children below 33 kg body weight.

Proposed SmPC wording for Baclofen Intrathecal

Section 4.1 Therapeutic indications

Paediatric population

Baclofen Intrathecal is indicated in patients aged 4 to <18 years with severe chronic spasticity of cerebral origin or of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) who are unresponsive to orally administered antispastics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses.

Section 4.2 Posology and method of administration

Baclofen Intrathecal is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, in implantable pumps suitable for continuous administration of Baclofen Intrathecal into the intrathecal space (EU certified pumps). Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with intrathecal bolus, followed by a very careful individual dose titration prior to maintenance therapy. Intrathecal administration of Baclofen through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience. Specific instructions for implantation, programming and/or refilling of the implantable pump are given by the pump manufacturers, and must be strictly adhered to.

Paediatric population

Screening phase

The initial lumbar puncture test dose for patients 4 to <18 years of age should be 25-50 µg/day based upon age and size of the child. Patients who do not experience a response may receive a 25 µg/day dose escalation every 24 hours. The maximum screening dose should not exceed 100 µg/day in paediatric patients.

Dose Titration phase

No proposed changes

Maintenance Therapy

The clinical goal is to maintain as normal a muscle tone as possible, and to minimise the frequency and severity of spasms without inducing intolerable side effects. The lowest dose producing an adequate response should be used. The retention of some spasticity is desirable to avoid a sensation of "paralysis" on the part of the patient. In addition, a degree of muscle tone and occasional spasms may help support circulatory function and possibly prevent the formation of deep vein thrombosis.

Paediatric population

In children aged 4 to <18 years with spasticity of cerebral and spinal origin, the initial maintenance dosage for long-term continuous infusion of Baclofen Intrathecal ranges from 25 to

200 mcg/day (median dose: 100 mcg/day). The total daily dose tends to increase over the first year of therapy, therefore the maintenance dose needs to be adjusted based on individual clinical response. There is limited experience with doses greater than 1,000 micrograms/day.

The safety and efficacy of Intrathecal Baclofen for the treatment of severe spasticity of cerebral or spinal origin in children younger than 4 years of age have not been established (also see section 4.4).

Section 4.4 Special Warnings and Precautions for use

For patients with spasticity due to head injury, it is recommended not to proceed to long-term Baclofen intrathecal therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Use of intrathecal Baclofen in the paediatric population should be only prescribed by medical specialists with the necessary knowledge and experience. There is very limited clinical data regarding the safety and efficacy of the use of Baclofen Intrathecal in children under the age of four years.

Proposed PIL wording for Baclofen Intrathecal

Please read this product information carefully before you or your child is given Baclofen Intrathecal since it contains important information.

1. What Baclofen and what is it used for

Your doctor has decided that you or your child needs this medicine to help treat your condition.

Baclofen Intrathecal is intended for adults and children of 4 years and above and is used to reduce and relieve the excessive tension in your muscles (spasms) occurring in various illnesses such as cerebral palsy, multiple sclerosis, spinal cord diseases, cerebrovascular accidents, and other nervous system disorders.

2. Before you take Baclofen

Children and adolescents:

Baclofen intrathecal formulation is intended for children of 4 years and above.

The applicant was requested to submit a Type IB C.1.3 variation to update the SmPCs and PILs of products containing the active ingredient Baclofen (oral and intrathecal formulations) in line with the above work-sharing recommendations within 90 days of this report.

I. INTRODUCTION

On 12 February 2009, one MAH submitted 18 completed paediatric studies for Baclofen, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. From the submitted studies 10 were performed by the MAH and 8 are published papers not sponsored by the MAH.

Short critical expert nonclinical and clinical overviews have also been provided.

The MAH stated that based on the review of the available data, no amendment to the existing Core Data Sheets is warranted.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies

Baclofen is currently globally marketed as oral tablets (5mg, 10mg, 25mg), oral solution (5mg/5ml) and intrathecal injection or infusion (50mcg/1ml, 10mg/20ml, 10mg/5ml). Different pharmaceutical forms have been used in the submitted clinical studies with protocol defined dose adjustments by the clinical researchers according the clinical response of the individual patients.

The MAH has provided short description of the medicinal product and its recommended indications and posology in children. Some variations in the indications and dosage recommendations are noted compared to the currently approved UK SmPC but separate texts from each MS were not submitted.

Baclofen is used in the following indications (wording provided in the MAH's overview paper) :

Tablets and Oral syrup:

"Spasticity of the skeletal muscles in multiple sclerosis. Spastic conditions occurring in spinal-cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin: e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasm of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease".

Intrathecal (IT) administration:

"Baclofen Intrathecal is indicated in patients with severe chronic spasticity of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) or of cerebral origin who are unresponsive to orally administered antispastics (including oral Baclofen) and/or who experience unacceptable side effects at effective oral doses.

For patients with spasticity due to head injury, it is recommended not to proceed to long-term Baclofen Intrathecal therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

A small number of patients with tetanus have been successfully treated with Baclofen Intrathecal to reduce hyperreflexia, clonus, and trismus."

Baclofen is given orally in tablet or liquid form and these 2 formulations are considered bioequivalent. The lowest dose compatible with an optimal response is recommended. Careful Baclofen

titration of dosage is essential. If too high a dose is initiated or if the dosage is increased too rapidly side effects may occur. Once the maximum recommended dose has been reached, if the therapeutic effect is not apparent within 6-8 weeks a decision whether to continue with baclofen should be taken.

Regarding the paediatric oral use of Baclofen, the MAH provides the following recommendations:

“Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), preferably in 2-4 divided doses. Therefore, Baclofen tablets are not suitable for use in children below 33 kg body weight.

The dosage should be raised cautiously, at about 1 to 2 week intervals, until it becomes sufficient for the child's individual requirements.

The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight.

The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

If no benefit is apparent within 6 to 8 weeks of achieving the maximum dosage, a decision whether to continue with Baclofen should be taken.”

There are 2 issues regarding oral administration of Baclofen. Firstly, with maximum tolerated doses, very little drug reaches the site of action in spinal cord. The mean plasma to CSF concentration ratio is approximately 8:1 (Knuttsen et al 1974). Secondly the amount of oral drug which can be given is limited by the sedative properties of the drug, particularly in patients with spasticity due to cerebral palsy (CP). Therefore using direct delivery of the drug to spinal cord with intrathecal administration might be a necessary therapeutic option in children as well as adults. For the intrathecal administration, the 50 micrograms/1ml intrathecal formulation is intended for administration in single bolus test injections via a lumbar puncture or intrathecal catheter and 10mg/20ml and 10mg/5ml solutions have been developed for use with implantable pumps. Each patient must undergo an initial screening phase to determine the response to test bolus doses followed by a dose-titration phase to determine the optimum dose schedule for maintenance therapy with an appropriate implanted delivery system. This is due to the great variability in the effective individual therapeutic dose.

Regarding paediatric use of this formulation, no dosing recommendations are provided by the applicant apart from the following statement, also included in the UK SmPC, section 4.4:

Precaution in paediatric patients

“Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. There is very limited clinical data on the use of Baclofen Intrathecal in children under the age of six. The safe use of Baclofen Intrathecal in children under the age of four has not yet been established.”

Assessor's Comment

The origin of the posology information provided by the MAH for the different formulations of baclofen is not clarified. Several points demonstrate the possibility of significant variation between national SmPCs as for example with those currently approved in the UK. In detail compared with the MAH provided information the following differences could exist between member states:

- Not all tablet sizes as well as the liquid formulation are approved in all MSs
- The initial dose is calculated by weight and divided in range of 2 to 4 doses.
- There is not information regarding taking the drug with meals.
- There is no information regarding administration of baclofen in patients that are fed through a gastrostomy tube

- The dosage should be carefully increased at intervals that range from just days (UK SmPC) to 1-2 weeks.
- Discontinuation of baclofen should be considered after 6 to 8 weeks of ineffective treatment
- Regarding intrathecal administration of baclofen, the UK SmPC in section 4.1 states that it is not recommended for use in patients under 18 years of age but it is unclear what the licensing status is in other member states.
- No paediatric dosing regime was provided by the applicant for the intrathecal administration.
- In the precaution of paediatric use of intrathecal baclofen, a cut-off age and weight should be included (minimum 15 kg weight and 4 years or age are mentioned in some review publications). As a conclusion in the rapporteur's opinion, intrathecal administration of baclofen represents a significant therapeutic benefit in the paediatric population with CP if safety and efficacy is demonstrated.

II.2 Non-clinical aspects

1. Introduction

No non-clinical studies on juvenile animals to investigate the effect of baclofen in the developing body and nervous system have been performed by the MAH.

The MAH submitted the following 2 reproductive and developmental toxicity studies:

1. Reproductive Study BA 34647 Segment I – rodent experiment #137- Effect on drug on fertility and reproductive performance
2. Reproductive Study BA 34647 Segment OOO – rodent experiment #142 - Perinatal and postnatal effects

Assessor's Comment

No literature review has been conducted by the MAH to identify preclinical studies relevant for the paediatric use of baclofen.

2. Non Clinical overview

The report provided by the MAH, summarizes the data for the above mentioned studies. In respect of the use of Baclofen in the paediatric population the report concludes that:

“The results of the toxicological investigations in the offspring of pregnant rats administered baclofen at doses up to 20 mg/kg/day showed that baclofen had no direct toxic effects on pup development.”

3. Non clinical studies

3.1 Reproductive Study BA 34647 Segment I – rodent experiment #137

➤ Description

A Segment I study was conducted to determine the effects of baclofen on fertility and reproductive performance in rats.

➤ Methods

Study design

Baclofen was administered orally in the diet at target dosages of 5 and 20 mg/kg/day to male rats 60 days prior to and during the mating period. The females were administered the same dose levels 14 days prior to mating and continued throughout the mating,

gestation and lactation periods. Approximately one-half of the females of each group were necropsied on day 13 of gestation and the other half continued on study and were allowed to have normal parturition. The pups were weighed at birth and 4, 14 and 21 days post partum.

➤ **Results**

No significant changes in feed consumption or body weights were observed in the male animals. Overall mating was not adversely affected by treatment. Except reductions in feed consumption and body weight gains during pre-mating period, the low dose of baclofen had no adverse effects on fertility, general reproduction performance and survivability of pups. The high dose of baclofen produced significant reductions in maternal food consumptions, accompanied by corresponding decreases in body weight gain during the gestation and lactation periods. The high dose treatment also produces a significant reduction of litter sizes and a statistical non-significant increase in the number of resorption and stillbirths. An apparent decrease in pup survival in the 20 mg/kg dose group was attributed to loss of the litters of three dams with agalactia and was not considered a direct effect of baclofen. Milk secretion also remained within normal limits as judged by the weight increases of the sucklings.

➤ **Conclusions**

In conclusion, this study demonstrated that mating ability and fertilization were not affected by treatment with Baclofen. In females baclofen generally decreased maternal food consumption and body weight gains. These decreases were dose related and in the high dose group were statistically significant. A drug effect on milk secretion was not likely, since weight increases in the suckling pups were not affected. Despite these changes the size and weight of the offspring were not affected and therefore the effect of the tested drug on the offsprings appears to be minimal.

3.2 Reproductive Study BA 34647 Segment OOO – rodent experiment #142

➤ **Description**

Perinatal and postnatal effects of baclofen were evaluated in a Segment III study in rats.

➤ **Methods**

Study design

Pregnant rats were administered baclofen at dose levels of 5 and 10 mg/kg/day from gestation day 15 through day 21 post partum. At birth, the number of neonates was recorded and each pup was weighed and examined for gross abnormalities. The litters were observed daily for clinical signs and mortality. Body weights were recorded on days 4, 14 and 21 post partum.

➤ **Results**

Five out of the 31 dams in the high dose group showed severe drug toxicity. From day 15 through to day 21 of gestation, no significant differences were found in the average weight gain or feed intake in the low dose group. Females in the high dose group showed significant reductions in both parameters. The number of stillborns was increased in both treatment groups but the differences compared to placebo were not statistically significant. Mean body weight of newborns in the 5 mg/kg group were similar to controls. A statistically significant decrease in mean pup body weight in the 10 mg/kg group was noted up to day 4 post partum but was similar to the control group by day 21 post

partum. The increased perinatal loss in the low dose group was not significant but was statistically increased in the high dose group.

➤ **Conclusions**

In this study lower doses (5 and 10 mg/kg) have been used to assess maternal and newborn effects of baclofen. Based on the results of this study, baclofen administered to rats at a dose of 10 mg/kg from day 15 of gestation through day 21 of lactation produced a significant reduction in maternal food consumption during gestation and consequent retardation of fetal growth which was manifested by reduced pup weight at birth. The significant decrease in pup survival from 24 hours to 4 days post partum at 10 mg/kg was attributed to the loss of entire litters from five dams that showed severe toxicity.

4. Discussion of non clinical aspects

The 2 nonclinical reproductive studies, Segment I and Segment III in rats, have examined the effects on the offspring of rats administered baclofen throughout the lactation period. Growth and development of pups were evaluated from birth until weaning. Placental transfer and milk excretion studies in pregnant rats showed that baclofen is distributed to fetal tissues via the placenta and is excreted in milk. The author of the preclinical report concludes that the effects observed on pup survival and growth in these studies were considered secondary to maternal toxicity at the high dosing regimes of 10 or 20 mg/kg.

Assessor's Comment

These 2 very old studies attempt to investigate the perinatal effects of different doses of baclofen in rats. The assessor agrees with the comment from the author of the overview that they were carried out before the Good Laboratory Practice (GLP) regulations in 1979 and therefore included fewer than expected subjects with design limitations. The selection of the dosing regimes was not analysed and although inspection for gross anomalies was mentioned, no data has been provided. It is noted that the UK SmPC states that Baclofen increases the incidence of omphaloceles (ventral hernias) in the foetuses of rats but not mice or rabbits when given in very high doses (13 times the maximum oral dose recommended for human use). The assessor is of the opinion that the data provided from this study do not provide any new relevant information for the paediatric population.

II.3 Clinical aspects

1. Introduction

Clinical development program of baclofen in paediatric patients has been completed for the indication of muscle spasm of cerebral origin, especially where due to infantile cerebral palsy, in the late seventies and early eighties. The MAH submitted the following 8 clinical studies investigating PK, efficacy and safety of baclofen in the paediatric population. It is noted that all of these studies have been conducted by the MAH:

Clinical pharmacokinetics study

Report of plasma baclofen levels in children receiving chronic intrathecal baclofen infusion.

Clinical efficacy studies

Trial # LI/IT8: Efficacy of daily intrathecal baclofen to treat children with severe spasticity.

Trial # NL/10: Statistical result of a double-blind comparative trial with Lioresal versus placebo in cerebral palsy in children.

Trial # G/D-85: Statistical results of a double-blind, between-patient comparative trial with Lioresal versus placebo in cerebral palsy in children.

Trial # G/DK-11: Statistical results of a double-blind, within-patient, comparative trial with Lioresal versus placebo in cerebral palsy in children.

Trial # B/4: Statistical results of a double-blind, between-patient, comparative trial with Lioresal versus placebo in cerebral palsy in children.

Trial # BR/2: Results of a double-blind, between-patient, comparative trial with Lioresal versus placebo in cerebral palsy in children.

Clinical safety study

Trial # 06/86: An open study, to assess the tolerability and acceptability of Lioresal Liquid in children when substituted for an equivalent dose of Lioresal tablets

Assessor's Comment

Please note that of the clinical efficacy studies, Trial # NL/10, Trial # G/D-85, Trial # G/DK-11, Trial # B/4 and Trial # BR/2 will be assessed jointly due to identified similarities.

Additionally the MAH has conducted a search of Medline which revealed 4 controlled trials of oral baclofen in children with CP from 1977 and 3 reviews. Hand-searching of reference lists produced 1 further open trial and 2 reviews. These studies are provided in the following references:

Reference	Type of publication
[Milla JP and Jackson AD (1977)]	Paediatric study
[Scheinberg A, Hall K, Lam LT, et al (2006)]	Paediatric study
Young (1980), as discussed in [Scheinberg A, Hall K, Lam LT, et al (2006)]	Paediatric study, confirms baclofen efficacy
McKinlay (1980), as discussed in [Scheinberg A, Hall K, Lam LT, et al (2006)]	Paediatric pharmacotherapy review, confirms baclofen efficacy
[Vargus-Adams JN, Michaud LJ, Kinnett DG, et al (2004)]	Paediatric pharmacotherapy review, confirms baclofen efficacy
[Zalman E (1976)]	Paediatric study
[Ebbutt AF and Jukes AM 1978]	Paediatric study
[Krach LE (2001)]	Paediatric pharmacotherapy review, confirms baclofen efficacy
[Albright AL (1996)]	Paediatric pharmacotherapy review, confirms baclofen efficacy
[Verotti A, Greco R, Spalice A, et al (2006)]	Paediatric pharmacotherapy review, confirms baclofen efficacy

2. Clinical overview

The report provided by the MAH summaries the data for the above mentioned studies. In respect of the paediatric population, the report states that there are no systematic studies in paediatric patients with baclofen conducted in patients with spasticity due to reasons other than infertile cerebral palsy (CP) which is one of the most common neurological diseases in children. It is concluded that:

“...since the recommended doses of baclofen produce systemic exposures in the paediatric population that are similar to those known to be associated with safe and effective treatment of these conditions in adults (multiple sclerosis, spastic conditions occurring in spinal-cord diseases as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease), and since the pathology in adults and children can be assumed to be similar, efficacy can be extrapolated from adult data.”

Assessor’s Comment

In the assessor’s opinion, the conclusion that the pathology of different types of neurological conditions manifested with spasticity is similar to adults and children is not acceptable as no evidence is provided to support it. Recent publications (Hagglund 2008) have been investigating the development of spasticity with age in children with CP, recognizing the fact that it is an evolving condition. The effect of baclofen as a muscle relaxant is established however systemic exposures of the drug in the paediatric population with different diseases appear not to have been investigated.

3. Clinical studies

3.1 Clinical pharmacokinetics study

Report of plasma baclofen levels in children receiving chronic intrathecal baclofen infusion

➤ **Methods**

- Objective
To measure the plasma baclofen concentration in children receiving long-term continuous intrathecal infusion of Baclofen Intrathecal.
- Study design
PK study.
- Study population /Sample size
6 patients with CP aged between 8-18 years.
- Treatments
All patients were receiving chronic intrathecal baclofen in the simple continuous infusion mode (dose range 77 to 400 µg/day) at a rate 3.22 to 16.7 µg/hr, using the SynchroMed infusion system with an intrathecal catheter located in the region of T10-T11. none of the patients was receiving concomitant anti-spasticity medications but 2 were receiving oral Tegretol.
- Outcomes/endpoints
Blood samples were drawn during outpatient visits at a minimum of 36 h after last dose adjustment. The concentration of baclofen in the study samples was determined by using a validate Gas Liquid Chromatography (GLC) assay with a limit of quantitation of 10 ng/mL.
- Statistical Methods
Statistical analysis not performed

➤ **Results**

Plasma Baclofen concentrations in all the six patients at 36 hr post dose of last dose were at or below the limit of quantitation (10 ng/mL) of the assay. It was concluded that

the low plasma level of baclofen is about 1/30 of the 300 ng/mL concentration following a 20 mg oral baclofen dose measured in adults (Knuttson et al 1974).

Assessor's Comment

Although the PK objective of the study is established, the implications for the clinical practice of paediatric intrathecal baclofen use are not clearly defined. The sample size is relatively small and there were no patients under the age of 8. The dosing range used is significantly lower than the current practice standards (*maintenance dose ranging from 24 micrograms to 1.2 mg daily in children under 12 years or 1.4 mg daily for those over 12 years*). The duration of the chronic treatment prior to the trial is not mentioned and there are no data regarding the type of CP, the severity of the condition and the maintenance of the therapeutic effects during treatment. In the assessor's opinion, this is a very limited study which does not offer robust evidence on the PK profile of chronic intrathecal use of baclofen in children.

3.2 Clinical efficacy studies

Trial # LI/IT8: Efficacy of daily intrathecal baclofen to treat children with severe spasticity

➤ Methods

- **Objective**
To investigate the effect of intrathecal (IT) baclofen on children with severe spastic quadriplegia related to cervical cord injury, cerebral palsy and head injury.
- **Study design**
Pilot study with a three stage design was followed: an open trial which allowed determination of most effective dose was followed by randomised, double blind crossover trial using baclofen and saline placebo to test the immediate efficacy of the treatment using the optimal baclofen dose. In the third stage, children shown to benefit from IT baclofen then entered a six months open trial, after insertion of a pump to provide a continuous intrathecal infusion of the drug. The rationale for this design was that it enabled the identification of children who appear to have significant clinical response and thereby limits the insertion of an infusion pump to these children.
- **Study population /Sample size**
Children aged 4-18 years with severe spastic quadriplegia related to cervical cord injury (n=1), cerebral palsy (n=3) and head injury (n=2).
- **Treatments**
Starting the day after the placement surgery, 50µg bolus dose of baclofen was given and each day following with the concentration increasing by 25µg every 24 hours to 100µg and then by 20µg every 24 hours to a maximum of 160µg. The decision regarding the optimal dose for the randomized trial was based on clinical examination with emphasis on tone and deep tendon reflexes. Two types of infusion systems were used and a brief assessment of their technological function was conducted by the authors. There have not been reported any problems with the placement of the pumps even in a child aged 4 years and no problems with the accurate delivery of the drug.
- **Outcomes/endpoints**
Primary outcomes assessed in this trial were Deep Tendon Reflexes, Lower Limb Tone and Patient response questionnaire, while secondary outcomes were Spasms, Range of motion, Myometry readings and Upper Limb Tone. Other assessments included a full physical and neurological status examination and physical growth parameters.

- **Statistical Methods**
Descriptive methods were used to summarize the results. Because of the variability of the patients, no attempt was made to perform statistical analysis.

➤ **Results**

- **Dose response trial**
One patient was discontinued from the trial as on the starting dose of 50µg he became markedly sedated. The remaining 4 patients responded to treatment with the maximum required dose ranging from 75µg to 180µg. At the identified doses, deep tendon reflexes in the lower limbs were eliminated and tone in the hip adductors was reduced in all patients. In all patients parents/caretakers felt there was a significant improvement in spasticity.
- **Double-blind trial**
One patient (the spinal cord injury patient) did not complete this stage because the catheter kinked during the trial. In 3 of the remaining 4 patients deep tendon reflexes were eliminated in the lower limbs and there was a significant reduction in tone. One patient did not respond to the intrathecal baclofen during the double blind trial despite the clear therapeutic effect during the dose response trial. The patients did enter the follow-up protocol.
- **Follow-up**
Two formal follow-up assessments were done over a 6 months period. Three out of four children who had distinct clinical response to baclofen in the second stage of the study continued the trial. All children had some degree of positive clinical response.
- **Adverse effects**
The major adverse effects of baclofen were sedation, bradycardia (n=2) and hypotension (n=2). These occurred primarily during bolus administration of the drug, either during the initial dose response phase or when a bolus was given on top of a continuous rate. A prolonged episode of seizures occurred in one patient who had previous history but was seizure free for 2 years. Another patient had a seizure while on anticonvulsants, having been seizure free for about 6 months. There were no cases of local infection or meningitis. However the authors mention a case of a patient who has developed symptoms and signs of meningitis in the “continuing study” without further details regarding this on going trial. The patient was successfully treated with antibiotics.

Assessor’s Comment

The sample size is very small and the design of the study limits the significance of the findings. However the authors attempt to provide a useful discussion of the different issues regarding spasticity in the paediatric population and the treatment benefits and complications with intrathecal baclofen. In particular, the difficulties in objective measurements of outcomes in this population and the lack of clearly defined guidelines of the dosing regime are reported. It is noted that after the initial period of escalating baclofen doses to maintain effect, the follow-up period is too short to determine maintenance of the therapeutic effect.

According to the authors’ conclusion, the clinical significance of the response varied among patients and children with cerebral palsy had a better response than the head injury children. In CP children, intrathecal baclofen appear to provide an effective treatment for muscle spasm of cerebral origin. In the assessor’s opinion, this study is too limited to offer robust evidence on the efficacy of intrathecal baclofen in paediatric patients but helps identify the complexity of spasticity.

Trial # NL/10: Statistical result of a double-blind comparative trial with Lioresal versus placebo in cerebral palsy in children

➤ **Methods**

- Objective
Evaluation of the effect of Baclofen on the disabilities due to the pyramidal spasticity in children suffering from CP.
- Study design
Double-blind between patient comparative trial of baclofen oral tablets versus placebo using increasing dosages of the trial medication. The duration of study was 4 weeks.
- Study population /Sample size
The minimum sample size per treatment group was defined to be 15 patients and patients were classified according their symptomatology and patients with muscle hypotonia or atonia were excluded. Past or present history of epilepsy was defined as and exclusion criteria. 40 children with common diagnosis of spastic diplegia or quadriplegia, in some cases with combination with extrapyramidal athetosis or dystonia of both sexes, aged between 6 and 20 years, were randomly allocated.
- Treatments
Increasing doses of baclofen tablets were used, starting with 5mg twice daily and the dose being increased until optimal therapeutic response which should be achieved by day 14 and then maintained until the end of the trial period. Reported average was daily dose of 60 mg per child.
- Outcomes/endpoints
Spasticity, extrapyramidal symptoms, clonus, biceps and quadriceps reflexes, walking ability, scissoring, impairment in passive physiotherapy, self help and manual dexterity were assessed (Day 1 and every 7 days). At the end of the trial, overall evaluations were carried out for each patient by the investigator, the physiotherapy and the nursing staff.
- Statistical Methods
The incidence of improvement and the overall results at the end of the trial were compared between the baclofen and the placebo group using Likelihood Chi² –tests. P=0.05 has been taken as the relevant level of statistical significance throughout the assessments of the symptoms.

➤ **Results**

- From the 40 patients enrolled, 16 patients with epilepsy had to be excluded from the statistical analysis based on the trial's exclusion criteria. Each group had 12 patients and the 2 groups were homogenous in their baseline characteristics.
- The optimal dosage of the trial medication, namely 6 tablets, was reached within 12 days in both treatment groups. 7 patients in the placebo group and 8 in the baclofen group received undefined concomitant medication.
- No unwanted effects were reported
- Only slight improvement, if any at all, on the individual symptoms was observed. The only significant improvements were recorded at the end of the 4 week treatment period with regard to the criteria severity of spasticity and biceps deep tendon reflexes.
- At the end of the trial the investigator judged that there has been a "good effect" of treatment in only one case in the placebo group. The investigator was willing to continue with treatment in 2/12 cases in the baclofen group in comparison with 1/12 cases for placebo. The physiotherapist and nurse considered that the child's condition has improved in 2/12 cases treated with baclofen and in 1/12 treated with placebo.

Assessor's Comment

It is noted the MAH has provided 2 documents for the above mentioned study of very poor quality, contradicting figures and summaries and has reached conclusions summarized in the clinical overview report that do not reflect the lack of therapeutic effect of baclofen in this study.

Trial # G/D-85: Statistical results of a double-blind, between-patient comparative trial with Lioresal versus placebo in cerebral palsy in children**➤ Methods**

- Objective
Evaluation of the effect of Baclofen on the disabilities due to the pyramidal spasticity in children suffering from CP.
- Study design
Double-blind between patient comparative trial of baclofen oral tablets versus placebo using increasing dosages of the trial medication. The duration of study was 4 weeks.
- Study population /Sample size
The minimum sample size per treatment group was defined to be 15 patients and patients were classified according their symptomatology and patients with muscle hypotonia or atonia were excluded. Past or present history of epilepsy was defined as and exclusion criteria. 32 children with common diagnosis of spastic diplegia, quadriplegia or hemiplegia, in some cases with combination with athetosis, dystonia or ataxia of both sexes, aged up to 13 years, were randomly allocated. The minimum age is not mentioned.
- Treatments
Increasing doses of baclofen tablets were used, starting with 5mg twice daily and the dose being increased until optimal therapeutic response which should be achieved by day 14 and then maintained until the end of the trial period. Reported average was daily dose of 60 mg per child.
- Outcomes/endpoints
Spasticity, extrapyramidal symptoms, clonus, biceps and quadriceps reflexes, walking ability, scissoring, impairment in passive physiotherapy, self help and manual dexterity were assessed (Day 1 and every 7 days). At the end of the trial, overall evaluations were carried out for each patient by the investigator, the physiotherapy and the nursing staff.
- Statistical Methods
The incidence of improvement and the overall results at the end of the trial were compared between the baclofen and the placebo group using Likelihood χ^2 –tests. $P=0.05$ has been taken as the relevant level of statistical significance throughout the assessments of the symptoms.

➤ Results

- From the 35 patients enrolled, 6 patients had to be excluded from the final evaluation due to suspected confusion between the trial preparations (n=3) or serious concomitant disease (n=3), leaving a total 29 cases for statistic evaluation.
- The optimal dosage of baclofen 30-40mg was reached within approximately 9 days. In the placebo group optimal dose was not reached in 10/15 cases compared to 6/14 in the

- baclofen group. 2 patients in the placebo group and 1 in the baclofen group received undefined concomitant medication.
- Unwanted effects were reported in 3 cases in the placebo group and in 6 cases in the baclofen group. The most frequent side effects were lack of concentration, tiredness and passivity.
 - A significant difference between baclofen and placebo was recorded only to the range of abduction of the legs and the impairment of self-help in the 4th week.
 - At the end of the trial the investigator judged that there has been a “good effect” of treatment in 4/14 cases in the baclofen group compared to 5/15 cases in the placebo group. The investigator was willing to continue with treatment in 7/14 cases in the baclofen group and in 8/15 cases for placebo. The physiotherapist considered that the child’s condition has improved in 10/14 cases treated with baclofen and in 4/15 cases treated with placebo.

Trial # G/DK-11: Statistical results of a double-blind, within-patient, comparative trial with Lioresal versus placebo in cerebral palsy in children

➤ **Methods**

- **Objective**
Evaluation of the effect of Baclofen on the disabilities due to the pyramidal spasticity in children suffering from CP.
- **Study design**
Double-blind within-patient comparative trial of baclofen oral tablets versus placebo using increasing dosages of the trial medication. The duration of study was 2 x 4 weeks and the patients were allocated randomly to baclofen or placebo for 4 week, followed by another 4 weeks in the alternative treatment group. It is noted that there was no wash-out period between the 2 treatment periods.
- **Study population /Sample size**
The minimum sample size per treatment group was defined to be 20 patients and patients were classified according their symptomatology and patients with muscle hypotonia or atonia were excluded. Past or present history of epilepsy was defined as and exclusion criteria. 30 children with common diagnosis of spastic diplegia or quadriplegia, in some cases with combination with athetosis, dystonia or ataxia of both sexes, aged up to 18 years, were recruited. The minimum age is not mentioned. 2 patients dropped out during the course of the trial, and the remaining patients were randomly allocated in the 2 treatment groups. It is noted that from the original 30 cases, 12 had a history of epilepsy and they should be excluded from the statistical analysis.
- **Treatments**
Increasing doses of baclofen tablets were used, starting with 5mg twice daily and the dose being increased until optimal therapeutic response which should be achieved by day 14 and then maintained until the end of the trial period. Reported average was daily dose of 60 mg and 90 mg.
- **Outcomes/endpoints**
Spasticity, extrapyramidal symptoms, clonus, biceps and quadriceps reflexes, walking ability, scissoring, impairment in active or passive physiotherapy and self help and manual dexterity were assessed (Day 1 and every 7 days for each treatment period). On

Day 28 and at the end of the trial, overall evaluations were carried out for each patient by the investigator, the physiotherapy and the nursing staff.

- **Statistical Methods**

There are 2 issues identified in this trial that was designed to follow a “cross-over” study design. First, there was no wash out period and because there was some evidence to suggest that patients were not the same at the start of the second treatment period as they were at the start of the first, the data from the end of the trial have to be excluded from analysis. Therefore comparisons between treatments have been only made within the first treatment period.

Secondly the type of data arising from this study i.e. qualitative rather than quantitative (changes ‘-, 0, +’ for each clinical parameter) preclude the use of parametric statistic. Thus all treatment differences have been evaluated using the Likelihood Chi²-tests. P=0.05 has been taken as the relevant level of statistical significance throughout the comparisons. In view of the small numbers of cases, the incidence of the changes within both treatment periods and treatment groups were added together. This procedure means that statistical significances which may probably result from evaluation, in fact over-assess the differences between the incidences. In a number of instances no test has been performed because the treatment differences are so small. In the interpretation of the results, the significances are to be considered as trends.

➤ **Results**

- From the 30 patients enrolled, 2 patients dropped out during the trial, leaving a total 28 cases for statistic evaluation.
- In the first treatment period only 4 patients reached a therapeutically optimal dosage, all in the baclofen group. Similarly in the second treatment period only 3 patients in the baclofen group reached an optimal dose.
- Unwanted effects were reported for the first and second treatment periods respectively. In the 1st treatment period 11 patients complained of at least one unwanted effect, 8 receiving baclofen and 3 on placebo. In the 2nd period, 8 patients had at least one unwanted effect, all of them on baclofen. The most commonly occurring unwanted effects were apathy, limpness, drowsiness and tiredness.
- 2 patients that withdrew during the trial, one due to a hip operation and the other was discontinued after 2 days of treatment in the 1st treatment period because of increasing severe drowsiness.
- Under baclofen, the severity of the spasticity was reduced. The biceps deep tendon reflexes were increased under placebo but baclofen had no effect on this parameter. The range of abduction of the feet was increased under baclofen and somewhat reduced under placebo. The impairment of active physiotherapy seems to have improved and there was seem to be a positive effect on the impairment of self help in patients under baclofen.
- There was a tendency for the physician, physiotherapist and nurse/parent to prefer baclofen at day 28. At day 56, baclofen generally was no better than placebo in comparison within patients but it was less tolerable than placebo. In the majority of the cases the investigator stated that he would not wish to continue with treatment.

Assessor’s Comment

It is noted the MAH has provided 2 documents for the above mentioned study without a clear description of the context of these documents in relation to the findings of the study.

Trial # B/4: Statistical results of a double-blind, between-patient, comparative trial with Lioresal versus placebo in cerebral palsy in children

➤ **Methods**

- Objective
Evaluation of the effect of Baclofen on the disabilities due to the pyramidal spasticity in children suffering from CP.
- Study design
Double-blind between patient comparative trial of baclofen oral tablets versus placebo using increasing dosages of the trial medication. The duration of study was 4 weeks.
- Study population /Sample size
28 children of both sexes, aged between 4 and 17 years (median 8.4 years) were randomly allocated either to baclofen or placebo. In this trial, 50% of patients were diagnosed as having mild symptoms of cerebral palsy (spastic symptomatology mostly quadriplegic in distribution). It is noted by the investigator that in some cases the diagnosis of CP was incorrect.
- Treatments
An incremental dosage scheme was followed with a median daily dose of 4 tablets with baclofen 10mg and 3 tablets for placebo. The maximum dose used was 60 mg and generally given to older children.
- Outcomes/endpoints
Spasticity, extrapyramidal symptoms, clonus, biceps and quadriceps reflexes, walking ability, scissoring, impairment in active or passive physiotherapy and self help and manual dexterity were assessed (Day 1 and every 7 days for each treatment period). At the end of the trial, overall evaluations were carried out for each patient by the investigator, the physiotherapy and the nursing staff.
- Statistical Methods
No mentioning of the statistical method used is provided in the summary report of this trial.

➤ **Results**

- No dose used was considered by the investigator to be the optimal one.
- Improvement on the symptoms was practically negligible in both sub-samples, excepting improvement with baclofen in biceps reflexes, where improvement meant restoration of normal tone.
- It is noted that the most discriminating judgement of efficacy was given by the parent or child. 6/14 cases thought they had improved with baclofen in comparison to 2/14 cases treated with placebo. The difference was not statistically significant.
- No unwanted effect was reported in the placebo group, while 10 of the 14 cases treated with baclofen complained of at least one unwanted effect, mainly drowsiness and nausea.
- 1 patient discontinued in the baclofen group because of a suspected unwanted effect and 3 patients in the placebo group for various reasons (too frequent assessments, bronchitis, deterioration while on trial).

Trial # BR/2: Results of a double-blind, between-patient, comparative trial with Lioresal versus placebo in cerebral palsy in children

➤ **Methods**

- Objective
Evaluation of the effect of Baclofen on the disabilities due to the pyramidal spasticity in children suffering from CP.
- Study design
Double-blind between patient comparative trial of baclofen oral tablets versus placebo using increasing dosages of the trial medication. The duration of study was 4 weeks.
- Study population /Sample size
36 children of both sexes, aged between 2 and 17 years (median 7.5 years) were randomly allocated to 4 weeks treatment with either baclofen 10 mg tablets or placebo.
- Treatments
An incremental dosage scheme was followed with a median daily dose of 7 tablets of both baclofen or placebo. Even at this dose, the investigator believed that the optimal daily dose was not reached.
- Outcomes/endpoints
Spasticity, extrapyramidal symptoms, clonus, biceps and quadriceps reflexes, walking ability, scissoring, impairment in active or passive physiotherapy and self help and manual dexterity were assessed (Day 1 and every 7 days for each treatment period). At the end of the trial, overall evaluations were carried out for each patient by the investigator, the physiotherapy and the nursing staff.
- Statistical Methods
No mentioning of the statistical method used is provided in the summary report of this trial.

➤ **Results**

- The optimal daily dose used was reached in only 2 patients, one in each treatment group; however in these two patients, the 'optimal' dose was found later to be insufficient and was increased further.
- Improvement on the individual symptoms was generally slight. No difference in improvement between the treatment groups were of clinical importance or of statistical significance.
- The various global assessments on efficacy made by the investigator, physiotherapist and nurse confirmed no systematic or practically important difference between the treatment groups.
- A significantly greater portion of the baclofen group manifested unwanted effects believed due to treatment (10/18 in baclofen group versus 2/18 in placebo group). These included headache, drowsiness, nausea, "nervousness" and general weakness.
- 2 patients discontinued treatment in the placebo group due to non-medical reasons.

Assessor's Comment

Overall the studies Trial # NL/10, Trial # G/D-85, Trial # G/DK-11, Trial # B/4 and Trial # BR/2 fail to demonstrate efficacy of oral baclofen in paediatric patients with CP. These are very old studies and the rapporteur agrees with the comment from the author of the clinical review that

they are of questionable quality and therefore the results should be carefully reviewed. The duration of the trials was 4 weeks which is considerably short given the nature of the condition studied. Epilepsy is considered as an exclusion criterion but patients with past history of seizures have been recruited and often included in the statistical analysis. The sample sizes are small and include a wide range of symptomatology regarding the diagnosed CP. The cross-over design does not include a wash out period and therefore results could not be analysed appropriately. There are no clear definitions of the grading scale of the symptomatology. Ashworth scale is commonly used but that is not clearly stated in the submitted protocols. The methodology of the clinical assessment is more qualitative than quantitative and the definition of the investigator for the global assessments (doctor, physiotherapist, nurse) is not standardized. No unknown side effects have emerged from these studies. There is still conflicting evidence regarding the effect of baclofen on epileptic patients. In conclusion the findings of these studies do not add new efficacy or safety data on the use of baclofen in paediatric patients.

3.3 Clinical safety study

Trial # 06/86: An open study, to assess the tolerability and acceptability of Lioresal Liquid in children when substituted for an equivalent dose of Lioresal tablets

➤ **Methods**

- **Objective**
To assess the tolerability and acceptability of Baclofen Liquid in children when substituted for an equivalent dose of Baclofen tablets.
- **Study design**
Single centre, open, within-patient substitution study of 8 weeks duration.
- **Study population /Sample size**
21 children 1 to 16 years of age (mean 8.8 years) and suffering from cerebral palsy (15), hemiplegia (4) and spasticity (2) were entered.
- **Treatment**
On entry to the study patients were given the same dose of Baclofen liquid as they were taking previously in tablet form and at the same intervals as before. Doses ranged from 5 to 60 mg per day.
- **Outcomes/endpoints**
Assessments were performed by the investigator on entry of the study and after 2, 4 and 8 weeks of treatment with Baclofen Liquid.
At week 2 the following were recorded:
 - The period of time for which the patients had accepted Baclofen Liquid
 - Difficulties reported with the liquid by parent/nurse
 - Details of any adverse reactions
 - The clinical condition of the patientAt weeks 4 and 8 the following were also reported:
 - The patients' preference of medication
 - The usefulness of the medicine dispenser
 - The willingness of the parent/nurse to continue using the medication dispenser or 5 ml spoon.

- Statistical Methods
No statistical analysis has been conducted in this trial.

➤ **Results**

- Adverse reactions
3 patients reported possible adverse reactions to Baclofen Liquid. One patient developed a scaly rash after 4 weeks of treatment and was withdrawn from the study. One patient reported less white teeth after 4 weeks treatment but no further discolouration of teeth was reported at week 8. The last patient reported headaches and dizziness after 2 weeks of treatment. Neither symptom was reported at week 4 or 8.
- Acceptance of Baclofen tablets and liquid
Of the 21 patients who entered the study, 18 were reported of having problems associated with swallowing the tablets. After 8 weeks of treatment 16/20 patients reported no problems in taking the liquid formulation. The majority of acceptability problems with Baclofen Liquid were most apparent during the first 4 weeks of treatment and were associated with the palatability of the formulation and stinging of the throat and/or tongue. In all but 2 patients, symptoms had subsided by the eight week of treatment.
- Difficulties with Baclofen Liquid reported by parent/nurse
After 2 weeks treatment, difficulties were reported in 3 patients. 2 were difficulties associated with the palatability of the formulation and the other was reported for a patient who had difficulties swallowing all fluids. After 8 weeks treatment problems were reported in 3 cases, only one of which was reported at 2 week (patient with fluid swallowing difficulties). The 2 other patients reported that one didn't like that rash and the other reported a sickly feeling after taking it.
- Changes in clinical condition during the study
Changes to the clinical condition during the study were reported in 14 patients, all of whom demonstrated an improvement in response to treatment with Baclofen Liquid. In all cases the change was of improved relief of spasticity although in one case the change was not of clinical benefit ("more floppy").
- Preferences for medication

	Week 4		Week 8	
	Patient	Parent/Nurse	Patient	Parent/Nurse
No preference	4	8	1	6
Tablet	7	5	7	3
Liquid	10	8	12	11

Assessor's Comment

The open design of this study limits the significance of its findings. Bioequivalence appears to have been tested only in healthy adult volunteers. All of the assessments conducted were subjective and descriptive, making comparisons to tablet formulation unfeasible. Therefore the results should be interpreted with care. The author agrees that the findings of improved clinical condition in a number of patients are difficult to explain in view of the bioequivalence of tablet and liquid formulation. The exact method of administration of the tablets (i.e. tablets crushed and mixed with food or drinks) could be a reason.

In the assessor's opinion this study does not demonstrate acceptability and equivalence of the Baclofen Liquid formulation compared to tablets, but due the design limitations, the information does not provide robust evidence relevant to current paediatric clinical practice.

4. Additional literature references

The following list of studies was submitted as under article 45 of the Paediatric Regulation by the MAH. These published studies were included in the assessment and they are summarized below.

Baclofen in the treatment of cerebral palsy.

Albright AL (1996) *Journal of child neurology*, Vol.11 Number 2, March 1996

The author reviews the use of baclofen, particularly intrathecal administration, in the treatment of cerebral spasticity, using literature references as well as experience from ongoing studies that were conducted in children with his participation.

A comprehensive review of the pharmacology of baclofen is provided. It was originally synthesized as an anti-convulsant. Baclofen is a gamma-aminobutyric acid agonist, acts at the spinal cord level to impede the release of excitatory neurotransmitters that cause spasticity. It is noted that it acts at bicuculline-sensitive GABA_A receptors which are widely distributed in CNS and this activity causes its side effects. Oral baclofen improves cerebral spasticity mildly, but its activity is limited because of its poor lipid solubility. Children vary considerably in their responsiveness to oral baclofen and tolerance has been reported after prolonged oral administration.

Although oral baclofen is not as effective for cerebral spasticity as it is for spinal spasticity, it is nevertheless one of the most commonly used medications to treat cerebral spasticity in children. Van Hemert (1980) assessed baclofen in double-blind trial of 35 patients (mean age 25 years). Spasticity improved in 16 of 18 patients, although it improved substantially in only one. Hattab (1980) summarized 16 European oral baclofen trials in 315 patients with cerebral spasticity, 63% of whom were less than 25 years old. Baclofen reduced spasticity in 80% of patients in the 10 trial that had control subjects and in all studies, baclofen was equal to or better than diazepam in controlling spasticity with fewer side effects and with no effect on seizure frequency.

Intrathecal baclofen for spinal spasticity has been first been reported in adults by Penn and Kroin (1985). In children the first case was reported by Dralle et al (1985). Zierski et al (1988) reported good results in 12 paediatric patients, but the effects were profound, possibly due to severe deformities. In 1992 Muller reported a European multi-institution study of 72 patients with cerebral spasticity, 20 of whom were less than 10 years old and in 139 patients with spinal spasticity. He concluded that spasticity was successfully reduced in 90-95% of all patients but did not report the paediatric findings separately.

The author of this review provides an overview of issues identified with intrathecal baclofen administration in children. Continuous intrathecal baclofen infusion has been used to treat cerebral spasticity in two patient groups: in older ambulatory children with inadequate underlying leg strength, and in patients with severe spasticity in both the upper and lower extremities. For the assessment of clinical condition and the therapeutic effects, the Ashworth score is used; significant response should be considered an average reduction in lower extremity tone in the scale by 1 or 2 points, depending on the investigator. Responsiveness to intrathecal baclofen is confirmed by test injections before insertion of a programmable subcutaneous pump. Side effects in the screening trials could occur including severe discomfort from multiple lumbar punctures, infections from testing subcutaneous catheters, lethargy, agitation and other neurological adverse reactions to baclofen. Continuous intrathecal baclofen infusion dosages vary from 27 to 800 micrograms/day using different pump techniques and a best practice guide is provided by the author. Patients treated by the author for up to 66 months have showed no evidence of tolerance. Continuous intrathecal baclofen infusion reduces spasticity in the upper and lower extremities, and improves upper extremity function and activities of daily living but has no effect on athetosis in the dosages used to treat spasticity.

Complications related to the intrathecal catheter occur in approximately 20% of patients, and infection requiring pump removal occurs in approximately 5%. If spasticity in the legs returns

during treatment, investigations are needed and are listed by the author, in order to verify the good position and function of the delivering system as well as the possibility of patient's complications including infections. Overdoses cause unresponsiveness and profound hypotonia that may require assisted ventilation for 12-36 hours. Although intravenous doses of physostigmine have been used, there are largely ineffective in serious overdoses. In adults there have not been reported apparent neurological damages after overdoses with intrathecal baclofen.

The author concludes that intrathecal baclofen is more effective than oral administration in treating spasticity of cerebral origin. Such a treatment is costly and is associated with risks. However it is concluded that is probably the treatment of choice for ambulatory patients with lower extremity weakness whose gait is impaired by spasticity.

Assessor's Comment

This is an old paper that summarized very comprehensively the effectiveness and complications of intrathecal baclofen. No studies have been identified by the author that compared the oral with the intrathecal treatment. The currently licensed use of intrathecal baclofen states that there is limited or no evidence of its use in children younger than 6 years. In the assessor's opinion this article does not add any new information on this paediatric subgroup (≤6 years).

United Kingdom therapeutic trial of Lioresal in the treatment of spasticity of cerebral origin.

Ebbutt AF and Jukes AM (1978).Cambridge Med Publ. 1978:109

The authors investigated the effect of oral baclofen in patients with voluntary muscle spasticity of cerebral origin

In an 8 week open study 46 patients age ranging from 1year to 30 years (mena12 years) were enrolled. The dosage recommended in the study deepened on the age of the patient. For children under 8 years of age a starting dose of 5-10mg daily was given in divided doses. This could be gradually inc4reased to a maximum of 30-40mg over a 2 week period. In adults a suggested scheme was 5 mg tid for 3 days, 10mg tid for 3 daysm15mg tid for 3 days and then possibly increasing to a maximum of 100mg daily. The mean time to reach the maximum dose was around 3 week for all age groups. Basic patient data were recorded at the initial assessment and the clinical condition was assessed again at 7,14,21,28 and 56 days. The degree of spasticity was assessed by the Ashworth scale and clonus, flexor spasms and associated pain were rated. The majority of patients were graded as 2 or 3 on the Ashworth scale with the spasticity been less severe in the youngest age group (0-8years).

Baclofen was shown to have a good effect in patients with moderate and severe symptoms improving in about 2/3 of the cases.

Clonus, flexor spasms and associated pain

Grade	Clonus		Flexor spasms		Associated pain	
	Pre-trial	Final visit	Pre-trial	Final visit	Pre-trial	Final visit
0. Nil	27	28	20	28	35	39
1. Mild	9	11	7	11	3	3
2. Moderate	7	3	11	4	6	1
3. Severe	2	1	7	2	1	0
Not reported	1	3	1	1	1	3
No. of patients	46	46	46	46	46	46

The results from the study showed a steady improvement of spasticity in the sample as a whole.

Changes on Ashworth Scale

Age group (years)	Changes from initial visit on Ashworth Scale*	No. of patients showing change at:				
		Day 7	Day 14	Day 21	Day 28	Final visit
0 – 8	– 3	0	0	0	0	1
	– 2	0	0	3	3	1
	– 1	4	8	6	8	7
	0	11	7	6	5	6
	+ 1	1	1	1	1	2
	Missing data	1	1	1	0	0
9 – 16	– 2	0	0	2	2	2
	– 1	2	7	7	8	8
	0	15	9	7	6	7
	+ 1	0	0	1	0	0
	Missing data	0	1	0	1	0
	17 +	– 2	0	1	1	1
– 1	1	2	4	4	3	
0	11	9	7	6	8	
+ 1	0	0	0	0	0	
Missing data	0	0	0	1	0	

- * – 3 = Improvement 4 → 1 or 3 → 0
- 2 = Improvement 4 → 2, 3 → 1 or 2 → 0
- 1 = Improvement 4 → 3, 3 → 2, 2 → 1 or 1 → 0
- 0 = No change
- + 1 = Deterioration 0 → 1, 1 → 2, 2 → 3 or 3 → 4

At the final visit the physician, parent or nurse and physiotherapist were asked to assess the patients' condition relative to the start of the treatment. These responses were better in the younger age groups where about 50% of the patients were better than pre-trial, whereas in the 17+ age group only about 30% of the patients were thought to be better. Only 2 patients were graded as worse but not unanimously by the assessors. The most commonly reported side effects were hypotonia, sedation, nausea and vomiting and diarrhoea. At each visit about 75% of the patients reported no side effects. As the trial progressed, the incidence of side effects dropped despite the gradual increase in dosage. 6 patients were withdrawn from the trial due to side effects, most commonly hypotonia, sedation and nausea.

Assessor's Comment

This study is limited to a small number of paediatric patients, has design limitations and does not prove additional information in the safety or efficacy of the paediatric use of baclofen.

Pharmacotherapy of Spasticity: Oral medications and Intrathecal Baclofen.

Krach LE (2001) Journal of child neurology, Vol.16 Number 1, Jan 2001

The author conducts an extensive review of spasticity and the therapeutic options available for its treatment.

Spasticity is commonly defined as velocity-dependent resistance to movement associated with exaggerated deep tendon reflexes. The presence of spasticity alone is not considered sufficient to warrant its treatment. Clinicians believe that in treating spasticity, functional improvements can occur, and contracture formation can be limited. Also, prior to instituting treatment, careful consideration must be given to whether the individual makes use of his or her spasticity for functional gain. Also, one must be sure that there are no other factors increasing spasticity that can be eliminated, including infection, pressure sores, fracture or dislocation and nutritional status. Once a decision is made to treat spasticity, a few drugs are available for consideration. These include benzodiazepines, baclofen, alpha-₂-adrenergic agonists, dantrolene sodium, and gabapentin. No medication has been universally effective in the treatment of spasticity and the treatment in children has not been well documented.

The following table summarizes the site/mechanisms of actions of these anti-spasticity medications:

<i>Medication</i>	<i>Site of Action</i>	<i>Mechanism</i>
Benzodiazepines	Spinal cord—presynaptic inhibition	Increase GABA affinity for GABA _A receptors
Baclofen	Spinal cord—presynaptic inhibition	Binds to GABA _B receptors
Dantrolene sodium	Skeletal muscle	Inhibits release of calcium at sarcoplasmic reticulum
Alpha ₂ -adrenergic agonists	Spinal cord	Hyperpolarize neurons, decrease excitatory amino acids Possible role of substance P
Gabapentin	Spinal cord?	Increases total central nervous system GABA

When reviewing Baclofen it is noted that its side effects include sedation, impairment of cognitive function, particularly confusion, memory and attention. It has also been reported to cause orthostatic hypotension, dizziness, weakness, and ataxia. Depression has also been reported as a side effect of baclofen. In the author's experience, it usually involves the exacerbation of a pre-existing depression rather than depression in an individual without any past history of it. There has been some controversy about baclofen's effect on seizure activity. There have been reports of increased, decreased, or no change in seizure activity. Acute discontinuation of baclofen may cause signs and symptoms of withdrawal. This syndrome can be quite severe and is reported with both oral and intrathecal baclofen. It includes a rebound increase in spasticity often accompanied by spasms, hallucinations, confusion, seizures (including status epilepticus), and temperature elevation. A prominent feature of intrathecal baclofen withdrawal is dysesthesia, particularly pruritis.

Most studies of oral baclofen for the treatment of spasticity have involved adults. Milla and Jackson (1977) reported a double-blind, crossover study of the use of oral baclofen in 20 children with cerebral palsy. Baclofen was superior to placebo in reducing tone and allowing both active and passive limb movement. Side effects were noted to be minimal and dose related. Physicians wished to continue the drug in 12 of the patients, physical therapists in 13, and parents in 14. They recommend initiating baclofen at a dose of 5 to 10 mg/d divided into three doses for children 2 to 7 years of age.

Regarding the intrathecal use of baclofen, the author states that a number of studies have shown that it is effective in tone reduction in spasticity of both cerebral and spinal origin. Campbell et al (1995) summarized the results of a number of studies. Decreased tone and spasms were noted in all of the studies reviewed. A placebo-controlled, double-blind study of children and adults with cerebral palsy has shown bolus administration of intrathecal baclofen to be effective in tone reduction (Gilmartin et al 1993). During the open-label, continuous-infusion phase of the study, subjects maintained tone reduction in their legs and experienced a reduction in arm tone as well.

Drug-related side effects are less common than with orally administered baclofen but may occur as well. These include changes in bowel or bladder function and impotence that appear to be dose related. Sedation, dizziness, weakness, nausea, and vomiting have also been reported. As with oral baclofen, this author has seen exacerbation of depression in those with a pre-existing history of depression. The author of this review concludes that there are a few studies involving children and the use of these medications but fewer that objectively evaluate for functional changes. Often, information from use in the adult population has been extrapolated to extend the use of these medications to children.

Assessor's Comment

This is a helpful review of the therapeutic options in children with spasticity. The unwanted effects mentioned in this paper are included in the currently approved SmPC. The assessor agrees with the conclusion of the author that "Additional objective evaluation of these medications and their effects in children will be helpful to the clinician".

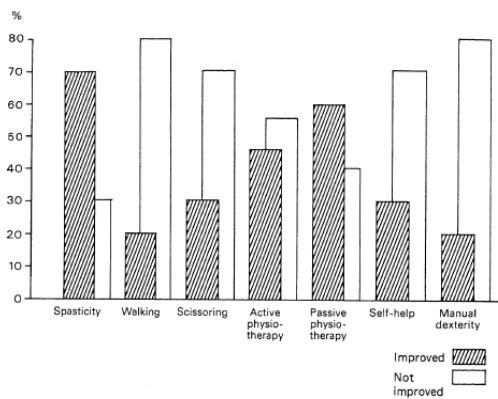
A controlled trial of baclofen in children with cerebral palsy.

Milla PJ, Jackson AD (1977). J. Int. Med. Res; 5: 398–404

A double-blind crossover trial was used to assess the effects of baclofen in comparison with placebo on the disability due to pyramidal spasticity in children suffering from CP.

20 patients aged 2 to 16 years were included; 5 were diplegic, 7 hemiplegic and 8 quadriplegic. History of epilepsy was an exclusion criterion. Patients received successive 4 week treatment periods of oral baclofen and matching placebo, the second treatment period starting immediately following the first. The first 2 weeks of each treatment period were for dose adjustments the initial dose of baclofen was 10mg daily in divided doses, which was increased in 3 increments over a period of 9 days, to a maximum daily dose of 60mg in children over 8 years and 30-40mg in children 2-7 years. Each patient was assessed at intervals of 7 days for spasticity, extrapyramidal signs, clonus, tendons reflexes, walking ability, scissoring, impairment in active or passive limb movements, degree of self help and manual dexterity. At the end of each treatment period, the clinician, the physiotherapist and the parent/nurse made independent overall evaluation of the patient's progress.

Taking the whole sample after 28 days treatment, 14 patients showed improvement while on baclofen compared to only 2 in the placebo group. The difference between the effects of treatment is statistically significant. There were no significant differences in walking, scissoring, self-help or manual dexterity. The following figure illustrates the number of children expressed as a percentage, who obtained improvement in the various clinical areas which were tested.



There was some suggestion that baclofen was of more benefit to the younger patients. The overall opinion of the doctor, physiotherapist and nurse/ parent demonstrates the superiority of baclofen. No side effects were noted in the placebo group but 5 patients experienced adverse reactions believed to be due to baclofen. These effects all occurred during the dose finding period and all occurred when baclofen was the first treatment. 4 patients had somnolence or sedation and 3 hypotonia. In all five, symptoms disappeared a few days after stopping treatment and the patients were later established on a lower dose of baclofen.

Assessor's Comment

The data produced by this study are limited to a small number of patients. The design of the study is not optimal as there is no wash-out period between treatment periods. The reported adverse events are known to be associated with the use of baclofen. The findings of this study do not add new efficacy or safety data on the use of baclofen in paediatric patients.

Oral baclofen in children with cerebral palsy: a double blind cross-over pilot study.

Scheinberg A, Hall K, Lam LT, O' Flaherty S (2006). J Paediatr Child Health. 2006;42(11):715-20

The aim of the study was to assess the effectiveness of oral baclofen in reducing spasticity and improving function in children with cerebral palsy.

The authors acknowledge that despite oral baclofen being one of the most commonly used medications used to treat spasticity in children, there are few published data on its effectiveness. Databases (Medline, Embase, CINAHL) were searched, revealing only one controlled trial of oral baclofen in children with CP by Milla and Jackson (1977). Hand-searching of reference lists produced one further double-blind cross-over trial (McKinlay et al 1980) and three open trials (Minford et al 1980), (Young 1980), (Vargus-Adams et al 2004). A brief synopsis of these papers is provided. A double-blind placebo controlled cross-over trial of 20 children aged between 7 and 16 years with spastic CP, McKinlay et al (1980), noted no significant benefit from baclofen. Assessments included muscle tone, clonus, extrapyramidal or cerebellar symptoms, manual dexterity, articulation and quality of gait. The researchers noted an 'unacceptable incidence of side-effects' (eight out of 20 on baclofen), including drowsiness, seizures and dizziness. The type and severity of CP in this group of children were not reported except that six of the 20 had an element of choreoathetosis and/or ataxia as well as spasticity. An open study of 15 children aged 4–15 years with hemiplegic CP was conducted by Minford in 1980, found significant decreases in hip and knee flexion at toe-off phase in both legs in the baclofen group; however, clinical improvement in gait occurred in only 5/15 (33%), and side effects were evident including sedation and deterioration of behaviour. Young (1980) reported a case series of 27 children aged 4 months to 12 years finding that the medication was most useful for clinical problems in younger 'double hemiplegic' children who had not yet developed fixed contractures, as nursing care was facilitated, and in 'pure diplegia', as mobility and wearing orthoses were improved. Based on these data the authors concluded that the evidence for the effectiveness of oral baclofen in both children and adults with CP is inconclusive.

The role of baclofen in seizure potentiation has been questioned. 10 The GABAB agonist action of baclofen may lead to inhibition of inhibitory inter-neurons and thus a shift to neuronal excitability. A recent retrospective case review reported that over a 2-year period, five of 54 children with CP or movement disorder aged 1–10 years who received oral baclofen developed new-onset seizures (Hansel et al 2003). But because children with severe CP already have a high underlying risk of seizures, the authors were unable to draw conclusions about the role of oral baclofen in seizure precipitation.

The investigators of this paper conducted a double-blind, randomised cross-over trial with a 2-week washout period in children 1-15 years (mean 7.4 years) between two study groups: group A received oral baclofen for 13 weeks followed by oral placebo, and group B received oral placebo followed by oral baclofen. For participants who were aged less than 8 years at the time of enrolment, the oral baclofen dose commenced at 2.5 mg daily, increased weekly over a 7-week period to 10 mg three times a day, and was then continued at that dose for the next 5 weeks. For those participants who were aged 8 or more years at the time of enrolment, the starting oral baclofen dose was 5 mg daily, increasing over a 9-week period to 20 mg three times a day, and was then continuing for the next 3 weeks at that dose. At the end of each 12-week period, the drug (either baclofen or placebo) was tapered over 6 days.

Baseline clinical and demographic data were recorded for each child including Gross Motor Function Classification System (GMFCS) level. The GMFCS is a five-level ordinal grading system found to be valid and reliable for children with CP aged 2–12 years. An experienced paediatric physiotherapist undertook all assessments including the modified Tardieu scores (MTS), Goal Attainment Scaling (GAS), and Pediatric Evaluation of Disability Inventory (PEDI). Assessments were performed at baseline and at the end of each 12-week period, prior to tapering of the drug. For parental satisfaction of the effects of the medication, a questionnaire was developed by the researchers and was administered to carers at the end of each 12-week period. The main focus in this assessment was whether carers would continue to use the prescribed medication.

Fifteen children with spastic or spastic/dystonic quadriplegia (GMFCS Level IV or V) were enrolled. Changes in the three domains of the PEDI (self-care, mobility and social function) between placebo and baclofen were small. Similar results were obtained for the modified

Tardieu ankle dorsiflexion scores with a mean change of -4.4° (-10.8° – 2.0°) and no significant treatment, carry-over and period effects found. For goal attainment scoring, there was a marginally statistically significant effect of baclofen treatment. Children on baclofen achieved better on the GAS compared with placebo. The most commonly set goals included improved transfers (six children), ease of use of walking frame (seven children), improved wheelchair positioning (five children), improved sleep (seven children), ease of positioning (six children) and improved upper limb function(nine children).

Results of the parent questionnaires revealed that 6 children experienced adverse effects on baclofen and 4 children experienced adverse effects on placebo. On the other hand, 7 children reported to have experienced positive effects on placebo and only 6 experienced some positive effects on baclofen. In this study, side effects associated with baclofen such as constipation, lethargy and seizures were evenly distributed between baclofen and placebo groups. During the study, only one child required dosage reduction because of drowsiness and at completion of the study that child was found to have been taking baclofen when the dosage reduction was requested. Another child was withdrawn because of seizures. As for the willingness to continue to use the prescribed medication, two-thirds of parents (n = 10, 66.6%) indicated they did not wish to continue with the placebo, and four indicated that they would continue. In comparison, eight (53.3%) did not wish to continue using baclofen and six (40.0%) indicated that they would continue baclofen.

It was concluded that this pilot study shows improvements within goals specific to children with severe disabling spasticity when taking baclofen compared with placebo. There was a lack of significant improvement in other outcome measures, the PEDI and MTS. Limitations of this study include a heterogeneous population, particularly with regards to age and the rather small sample size.

Assessor's Comment

This is a helpful review of the existing literature on treatment with baclofen of children with spasticity. The data produced by this study are limited to a small number of patients. A positive effect on daily functions of severely disabled children has been demonstrated. The unwanted effects mentioned in this paper, particularly seizures are included in the currently approved SmPC. The assessor agrees with the conclusion of the author that "Further research evaluating different dosage regimens and side effect profiles in larger groups of patients may also benefit clinicians using this drug in their daily practice."

Effects of oral baclofen on children with cerebral palsy.

Vargus-Adams JN, Michaud LJ, Kinnett DG, McMahon MA, Cook EF (2004). Dev. Med. Child Neurol. 2004; 46: 787-9

The authors investigated the use of baclofen through a prospective, uncontrolled, clinical trial. Participants were eleven children 3-5 years (mean age 4.3years) with moderate CP, as defined by their Gross Motor Function Classification System scores of II, III, or IV. Before receiving baclofen, each patient underwent a baseline assessment, including the Gross Motor Function Measure (GMFM), physical examination, and parent questionnaires.

The patients then went through dose escalation and continued treatment with oral baclofen for a total of six months. At that time, a follow-up assessment was performed with the same measures. Most patients reached a dose of around 2mg/kg/day of baclofen.

Five patients experienced sleepiness that usually resolved without dose alterations. There were no adverse events that were directly attributable to patients' baclofen treatment. One patient had new onset seizures while on 0.5mg/kg/day of baclofen and another had an exacerbation of her seizure disorder.

Patients demonstrated smaller gains on the GMFM-66 than expected, although this did not reach significance with a stratified t-test. Only two patients demonstrated greater than expected

improvement in their GMFM-66 score. Equal numbers of patients demonstrated increases and decreases. Range of motion and spasticity, assessed by goniometry and modified Ashworth scale, did not change. On several Child Health Questionnaire subscales, including Physical Summary, Role-Physical, and Bodily Pain, patients' scores decreased. This reflected poorer health status following baclofen treatment, but these changes were not statistically significant.

Ten parents reported that their child's functioning was improved while taking baclofen, four felt that their child was more comfortable, and six found that it was easier to care for their child. Sleepiness was noted to have worsened in four patients, improved in one, and was unchanged in the remainder. Eight of 11 patients continued to be treated with baclofen after completion of the study.

This uncontrolled study did not provide objective support for the use of oral baclofen among young children with spastic CP. The only meaningful positive changes were observed through parent reports. Baclofen may have had negative effects on motor function, as the patients did not demonstrate functional gains reported in similar children with CP. Several of the outcomes reflected worsening function or quality of life; however, these changes did not reach significance, potentially due to type 2 error.

The author concluded that "This study suggests that baclofen may impair motor progress or reduce quality of life parameters".

Assessor's Comment

This study did not demonstrate a positive effect on spasticity in very young children (3-5years) however positive changes were documented through parents' reports. The data produced by this study are limited to a small number of patients. Baclofen was well tolerated. The assessor does not agree with the conclusion of the author regarding impairment of motor progress or reduce quality of life following treatment with baclofen. Selection of the patients and the functioning aims of treatment are paramount in the disabled children with spasticity, as mentioned in Krach's paper (2001).

Pharmacotherapy of spasticity in children with cerebral palsy.

Verrotti A, Greco R, Spalice A et al (2006) *Pediatr Neurol* 34:1-6

The purpose of this article is to provide an overview of available oral and parenteral drugs for treatment of spasticity in cerebral palsy and to outline indications and contraindications.

It is summarized that in children, the most common aetiologies for cerebral palsy are traumatic brain injury, perinatal hypoxic-ischemic encephalopathy, encephalitis, cerebrovascular accident, and brain tumours. Among the available therapeutic options, intrathecal baclofen is one of the most effective substances that can reduce spasticity significantly in the upper and lower extremities. This therapy can be administered also in young children, but the patient's size is important (minimum 15 kg body weight). By infusing baclofen directly into the subarachnoid space around the spinal cord, potentiation of GABA-mediated inhibition of spasticity can be achieved while minimizing side effects secondary to high levels of baclofen in the brain. Intrathecal infusion of baclofen may be varied through the day to accommodate the patient's complete activities. The drug dose is not related to age or weight, and a gradual increase during the first 6-9 months is required. Generally, patients with ventriculoperitoneal shunts require lower doses. Some aspects of speech, communication, and saliva control seem to have improved, with bowel movement frequency decreased in some children receiving intrathecal baclofen; moreover, few changes in feeding and nutritional status have been reported. The majority of patients will sustain improved range of motion, decreased painful muscle spasm, and improvement in measures of independent function. Finally, this treatment may be associated with possible complications. Some studies suggest that children of younger age, as well as those with gastrostomy tubes and non-ambulatory status, were more likely to encounter complications necessitating explantation such as pump pocket collections and infections.

Infection may remain isolated to the pump pocket or may track along the catheter, with consequent meningitis.

Assessor's Comment

This is a helpful review of the therapeutic options in children with spasticity. The assessor agrees with the conclusion of the author that in carefully selected patients intrathecal baclofen is one of the most effective treatment options for treating generalized spasticity.

Motorische Störungen im Kindes-und Jugenalter. (Treatment with baclofen in spinal and cerebral spasticity)

Zalman E (1976). Artzl. Prax. 1976;64:2345

Article in German – Translation provided by the MAH.

The author provides that findings of his own experience in using oral baclofen in adults and children with spastic syndromes.

A total of 46 patients 3 to 27 years of age (mean 15 years) were treated with oral baclofen. The starting dose was 0,3mg/kg daily in 2-3 divided doses. After 14 days the daily dose was raised by 0.3mg/kg and after 1 to 2 months an average dosage of 1mg/kg daily was reached. The individual maintenance dosage ranged from 0.75 to 1.6 mg/kg daily. The duration of treatment in these patients was 3-27 months (mean 15months). The investigator states that the first effects were usually observed after a few weeks, at the time when the dose was around 0.5mg/kg daily. In an assessment scale from 1 to 6(1= very good response, 5=no change, 6=deterioration) the results revealed an improvement in 72% of the cases.

		Result of therapy					
		1.	2.	3.	4.	5.	6.
1. Hyperkinetic syndrome	(4)	0	3	0	1	0	0
2. Spastic syndrome	(38)	2	12	13	7	3	1
3. Atactic syndrome	(4)	0	0	3	1	0	0
Total	(46)	2	15	16	9	3	1
			<u>72 %</u>		<u>20 %</u>	<u>8 %</u>	

In a few cases treated with Baclofen the investigator observed a marked psychotropic action with improvement in behavioural disturbances, in aggression and in mood, with a better integration into the social surroundings. Side effects were observed in 6 patients (13%). Treatment was discontinued in 3 patients: one patient reported deterioration of ataxia with impaired balance, one had reoccurrence of epileptic attacks and the last had affective depressive disturbance with loss of appetite.

Assessor's Comment

This is a very old study. The baseline demographics of the patients including initial diagnosis and assessments are provided. The results in children are not analysed separately from the adults. The findings of this study do not add new efficacy or safety data on the use of baclofen in paediatric patients.

5. Discussion on clinical aspects

In the submitted studies, the key problem of paediatric spasticity is reviewed. It is evident that the efficacy of orally administered antispastic agents including baclofen is weak. There is fine balance between appropriate dosing and side effects. All the published articles conclude that baclofen should be used with caution in the mobile spastic patient, because the decrease in muscle tone may seriously impair movement performance. Only when the patient is totally dependent because of severe spasticity may it be advisable to improve spasticity even at the

cost of undesirable weakness or drowsiness. Intrathecal administration of baclofen appears to be more effective and better tolerated. However the lack of paediatric studies limits its use in children.

Based on a review of the submitted data there were no new major findings bearing on the overall safety profile of baclofen. Research on effect of baclofen on epileptic seizures up to this day inconclusive and special warnings are currently included in sections 4.4 and 4.8 of the SmPC. No changes regarding the safety of baclofen were recommended.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATIONS ON DAY 89

After the review of the submitted data in this article 45 European work-sharing procedure, the rapporteur agreed with the MAH that the data from the submitted studies did not specifically indicate any need of major change the current paediatric information in the SmPCs/PILs of Baclofen containing products.

However, the precise wording of all European national SmPCs was not provided by the MAH, and in the review provided by the MAH, it was unclear whether all European countries where baclofen is approved have similar posology recommendations for the paediatric patients.

The Applicant was requested to review the national SmPCs as well as all other available data which should form a basis for a proposed harmonised SmPC text regarding paediatric indications and dosage recommendation. Points of harmonization should take into account the following:

- Overall it appears that baclofen has only been studied in children with cerebral palsy. In other neurological conditions associated with spasticity (i.e. multiple sclerosis spastic conditions occurring in spinal-cord diseases as well as following cerebro-vascular accidents or in the presence of neoplastic or degenerative brain disease) extrapolation from adult use is not considered optimal. This should be appropriately reflected in the SmPC with clear separation of the paediatric indications.
- For oral administration, single proposals should be made for the number of daily divided doses (currently ranges between 2 to 4), the time intervals for incrementing the dosage (currently range from a few days to 1-2 weeks), the total daily dose in children per age and time for discontinuation of baclofen if there is not therapeutic effect (currently ranges from 6 to 8 weeks).
- From intrathecal administration the MAH should review current literature of paediatric studies and provide a comprehensive overview of the findings stratified by age. If no data is available, then a warning should be included in section 4.1 that Baclofen intrathecal is not recommended for use in patients under 4 or 6, depending on the available information. Harmonization of the dosing regime should also be proposed by the applicant regarding testing doses and maintenance therapy as well as duration of treatment.
- As baclofen is currently used off-label intrathecally in children within specialised centres for the treatment of generalised spasticity, the MAH could explore this opportunity for proactive collection of data relating to the paediatric use of this drug, including dosing protocols, safety and effectiveness, through setting up a registry.

Following circulation of the draft preliminary paediatric assessment report (Day 70 report), comments were received from MSs which were circulated to the MAH with the request to address these points individually when providing the response. The final preliminary PdAR (day 89) was circulated to the MAH in June 2009.

IV. MAH RESPONSE TO THE PRELIMINARY PDAR DAY 89

The MAH submitted a response to the Preliminary PdAR, dated 8/12/2009. In the cover letter the MAH stated that following receipt of the report, the MAH contacted their USA license partner, who is also the manufacturer of a dispenser pump for intrathecal use. The MAH was provided with additional data relevant for paediatric use of the intrathecal formulation which were submitted as part of the response document.

The MAH response package consisted of the detail response document to recommendations raised by the rapporteur and CMSs in the PdAR. The MAH's Core Data Sheets for Baclofen intrathecal ampoules (0.05mg/ml, 0.5mg/ml and 2mg/ml) and tablets (Baclofen 5mg, 10mg and 25mg) and syrup (Baclofen 1mg/ml) were also provided. Study reports for 11 additional MAH sponsored clinical trials were also submitted as well as a Critical Expert Overview of the studies regarding the use of intrathecal Baclofen in the paediatric population. Finally an extensive review of the literature was conducted by the MAH in order to identify currently available information regarding the paediatric use of ITB.

As a result of new data presented, the MAH proposed changes to the SmPC of Baclofen formulation for intrathecal use, and changes to the SmPC and PIL of oral formulations specific for use in the paediatric patient population.

IV.1 MAH CLINICAL STUDIES OF INTRATHECAL BACLOFEN IN PAEDIATRIC PATIENTS

1.1 Information on the pharmaceutical formulation used in the clinical studies

The information currently included in Core Data Sheet was provided by the MAH. It is noted that this information is not necessarily reflected in all national SmPCs.

1.2 Clinical studies of intrathecal baclofen

The following list was submitted by the MAH containing the additional sponsored clinical studies including paediatric patients receiving intrathecal Baclofen therapy by the MAH's USA partner:

Trial # VI: Report of a single center, double-blind placebo controlled trial of baclofen injection for spasticity of cerebral origin (Physician sponsored IND and Medtronic sponsored IDE)

Trial # VIII: Intrathecal baclofen for the treatment of spasticity of cerebral origin and other movement disorders

Trial # X: Intrathecal baclofen for treatment of spasticity of cerebral origin

Trial # XI: Medtronic multi-center study of the administration of intrathecal baclofen for the management of spastic Cerebral Palsy

Trial # XII: Intrathecal baclofen for treatment of spasticity in children

Trial # XIII: Intrathecal baclofen for the treatment of dystonia

Trial # D92-036: Surveillance program of Lioresal Intrathecal (baclofen injection) for spasticity of spinal cord origin

Trial # D96-056: Surveillance program of Lioresal Intrathecal (baclofen injection) for cerebral origin spasticity

Trial # D97-062: SynchroMed 10 ml pumps post-approval study

Trial # NVD94-043: Investigation of the administration of Lioresal Intrathecal (baclofen injection) for the management of spasticity of Cerebral Origin Treatment: IND protocol

2008 Annual Report, Implantable Systems Performance Registry (ISPR) Protocol NSP 0010-10000 (March 11, 2009)

Assessor's Comment

It is noted that in the submitted package, sufficient detail is only available for 6 out of the 11 studies (Studies VI, XI, D92-036, D92-056, D97-062 and the ISPR Report). The rest of the trials are not presented in detail but only as pooled data. Therefore evidence from them is difficult to interpret specifically for the paediatric population. Furthermore among the submitted studies only Trial D97-062 and the ISPR Report recruited exclusively paediatric patients (less than 18 years of age). The rest of the trials were carried out with adults and children grouped together.

1.2.1 Clinical Efficacy studies conducted in paediatric population with spasticity of cerebral origin

Medtronic-sponsored studies of intrathecal Baclofen (ITB) therapy in paediatric patients with severe spasticity of cerebral origin were conducted from the late 1980s through early 2000s. The results of these studies were summarized by the applicant in the critical expert overview document.

Trial # VI: Report of a single-centre, double-blind placebo controlled trial of baclofen injection for spasticity of cerebral origin.

This single-centre study used a two-phase design to evaluate the safety and efficacy of ITB. In phase one a controlled, randomized, double-blind screening trial was performed using baclofen injection and placebo (sodium chloride injection). In phase two the subjects who had a positive response to phase one entered an open label trial of continuous infusion of baclofen injection using the SynchroMed Infusion System. Eighty-two (82) patients between 4.3 and 35.8 years of age (median 13.2 years) were enrolled in phase one with diagnoses of spastic CP (n = 70), head injury (n = 6), Spinal Bifida (n = 1), encephalitis (n = 1), degenerative brain disorder (n = 1), CP dystonia (n = 1), Transverse Myelitis (n = 1), and Hallervorden Spatz syndrome (n = 1). Of the 82 patients enrolled, 64 were evaluable at the end of phase one and 53 went on to phase two and implant.

The average Ashworth Score at baseline (n = 51) was 3.01 and dropped to 1.85 (n = 22) at 27 months post implant. The longest follow-up in this study was 69 months. No deaths or permanent adverse sequelae occurred in this study. Forty-three (43) subjects experienced one or more of the 158 reported adverse events.

The MAH concludes that based on this study, ITB was proven to be effective in reducing cerebral origin spasticity in the lower extremities and did not present unreasonable risks in the patient population studied. In addition there was no evidence of tolerance or tachyphylaxis to ITB over a 24-month follow up period.

Assessor's Comment

The assessor agrees with the MAH that in this trial, the efficacy of ITB has been clearly demonstrated during the double-masked screening period. Highly significant reductions from baseline in the mean Ashworth scores were documented at 2,4,6 and 8 hours following a single dose for all three dose levels (25, 50 and 100 mcg). Furthermore, this beneficial effect was sustained during the open-label follow up period following implantation of a SynchroMed infusion pump.

With the exception at 45 months post-implant, the average daily dose has remained relatively stable over the reporting period with only a slight increase observed. Again, with the exception of 45 month follow-up, average daily doses were below 353 mcg. This pattern held through 63 months follow-up.

Regarding safety, there was no evidence of tolerance or tachyphylaxis to ITB over a 24 month follow-up period. The most common AEs for the baclofen group was nausea and vomiting in the

screening and implant phases. According to the investigator, this was largely attributable to spinal fluid loss. All patients recovered from adverse events with no permanent sequelae. Limitations of this study are that adult and children data were grouped together and no direct statistical comparisons were carried out for the age strata groups. Furthermore the primary diagnosis of patients was not homogenous. However, even with these limitations, the study provides convincing data about safety and efficacy of intrathecal baclofen use in the population examined.

Trial # XI: Medtronic multi-center study of the administration of intrathecal baclofen for the management of spastic Cerebral Palsy.

This was a multi-centre study designed to evaluate the safety and efficacy of ITB during a randomized, placebo-controlled, double-blind screening trial and during open label, long-term infusion. As in the previous study, in phase two the patients who had a positive response to phase one entered a 12 month, open label trial of continuous infusion of baclofen using the SynchroMed Infusion System.

In phase two the dosing was defined in the protocol. The initial daily dose of ITB administered by the implanted pump was based on the response to the screening dose. The pump was programmed to deliver a continuous daily dose equivalent to the minimum effective screening dose if the effect lasted more than 12 hours, and two times the effective screening dose if the effect lasted less than 12 hours. No dose increases were made in the first 24 hours to allow drug steady state to be achieved. The daily dose could be increased up to 40% every 24 hours until the daily dose reached three times the effective bolus dose.

Fifty-one (51) CP patients between the ages of 4 and 31.3 years (median 10.3 years) were enrolled in phase one. 43 subjects were implanted and followed in phase two.

In this study, efficacy of baclofen was demonstrated by clinically and statistically significant responses from baseline at 4 hours post injection compared to placebo, as measured by the Ashworth scale for spasticity in the double-blind, placebo-controlled phase.

Of the 51 patients, 41 patients (80.3%) exhibited a clinically significant response with a 50 mcg bolus dose. 10 patients went on to receive 75 mcg bolus, and 2 of those patients went on to 100 mcg screening boluses due to inadequate response. As with patients with spasticity of spinal cord origin, the 50 mcg bolus screening dose was the appropriate screening dose. In this patient population, the average daily dose of baclofen was 78.7 mcg at implant. Follow-up doses gradually increased from 176.4 at 3 months (N=35) to 304.5 at 12 months (N=19). Generally, the maintenance baclofen dose was lower than that seen in patients with spasticity of spinal origin.

No deaths or permanent adverse sequelae occurred in this study. Forty (40) subjects experienced one or more of the 138 reported adverse events. 15 patients (29.4%) experienced at least one adverse event in the double-blind screening phase. During long-term infusion, 31 (72.1%) patients experienced at least one adverse event. 3 patients had overdose caused by programming errors during drug concentration changes. These adverse events were successfully managed with hospitalization and temporary drug stoppage. All patients continued drug therapy without permanent sequel.

Assessor's Comment

Based on this study it is difficult to draw any significant conclusion from the comparison between cerebral and spinal origin of spasticity as the MAH attempts to do. As mentioned in the relevant literature, the clinical goals are often different between these groups and the individual patients. The reason is that some patients need to maintain a certain amount of muscle tone for ambulation, while in other patients, the clinical goal is to reduce spasticity for ease of care as it is often the case in paediatric CP patients. There is clear evidence that individual judgement of titration is needed to achieve the desired clinical effect. The findings from this study imply that the dose of ITB tends to gradually increase with chronic dosing over 12 months follow-up; however, Trial VI did not show such evidence of increase over a 36 months follow-up period.

The rapporteur concludes that as the data is not stratified by age group, they should be interpreted with caution regarding the proposed chronic titration of ITB in the paediatric population.

It is noted that the following studies VIII, IX, X, and XII presented below have not been analyzed separately. Overall the data from studies VI, VIII, IX, X, XI, XII, and NVD94-043 were pooled and analyzed together. No results have been provided individually for studies VIII, XII and NVD94-043.

Assessor's Comment

The justification for the pooling of the study results is not explained by the MAH. As sufficient detail is only provided for only 2 studies VI and XI and the rest of the trials were only presented as pooled data, it are significant limits in interpreting the relevant information for the paediatric population. Furthermore three of these studies (IX, X, XIV) recruited adult patients only, further diluting the robustness of the provided evidence. Trials VIII, X, XII and XIII included children in their recruitment process, however individual result reports of these studies are not provided by the MAH, merely the summary of the studies' design and results. Finally patients enrolled in Protocol XIII (the Dystonia study) are not included in this section; data from these subjects were only used as safety information because the MAH argues that the screening and dosing procedures were different from the other cerebral origin studies.

Trial # VIII: Intrathecal baclofen for the treatment of spasticity of cerebral origin and other movement disorders

This was a single-centre double-blind, placebo-controlled, cross-over study. Prior to pump implantation patients had to demonstrate response to a 100 mcg single bolus of baclofen injection. Following implantation patients were randomized to receive treatment with baclofen injection or placebo for a month which was alternated the following month. Those who responded to the baclofen injection continued to long-term therapy.

Trial # IX: Lioresal (baclofen) injection for intrathecal administration by the SynchroMed infusion system for severe spasticity of cerebral origin

This was a single-centre open-label study with a long term follow-up period. Patients were screened with up to three bolus doses of baclofen injection (50, 75, or 100 mcg). Those patients who had a 2 point drop in their Ashworth or Spasm scale score for a minimum of 4 hours went on to receive long term therapy.

Trial # X: Intrathecal baclofen for treatment of spasticity of cerebral origin

This was a single-centre double-blind, placebo-controlled, cross-over study. Patients were randomized into one of three groups getting a series of three injections (50 mcg, 100 mcg, placebo) at 24-hour intervals. If they had a two-point drop in their Ashworth or Spasm scale score for a minimum of 4 hours after the 50 mcg bolus a placebo dose was substituted for the 100 mcg bolus. patients who achieved a positive response went on to implantation.

Assessor's Comment

It is noted that Trials IX and X did not include paediatric patients and therefore the results are not considered relevant to this paediatric assessment report.

Trial # XII: Intrathecal baclofen for treatment of spasticity in children

This was a single-centre double-blind, placebo-controlled, cross-over study. Subjects were randomized to get a 50 mcg or placebo bolus on days 1 and 2 in a cross-over design. If they had no response they were randomized to 75 mcg or placebo on days 3 and 4. If they still had no response they were randomized to 100 mcg or placebo on days 5 and 6. Children under the age

of 5 could receive 25 mcg, 50 mcg, or 100 mcg in above pattern. Subjects with a positive response could go on to implantation.

Trial # NVD94-043 Investigation of the administration of Lioresal Intrathecal (baclofen injection) for the management of spasticity of Cerebral Origin

This was a multi-centre, open label study with long term follow up. Subjects were screened with up to three bolus doses of baclofen injection (50, 75, 100 mcg). Those who had a one point drop in their Ashworth score went on to long term therapy.

Seventy-four (74) subjects between 4.4 and 48.3 years of age were enrolled in this study with diagnoses of spastic CP (n = 37), brain injury (n = 28), anoxia (n = 2), arteriovenous malformation (n = 1), anoxia (n = 1), near drowning (n = 1), cerebral ataxia (n = 1), brain stem infarct (n = 1) and Wilson's disease (n = 1).

Trial # XIII: Intrathecal baclofen for the treatment of dystonia

This was a single centre, open label physician sponsored study. Subjects were screened with continuous intrathecal baclofen for 1-5 days through a percutaneous catheter connected to an external pump. For up to 10 days the dose was adjusted every 12 hours until a response was seen. Movement was recorded using video and scored by a third-party evaluator at baseline and after screening. Long term therapy was initiated if a positive response to the screening was observed.

Fifteen (15) dystonia subjects between the ages of 3.9 and 42.3 years (median 12.3 years) were enrolled in the study. Of the 15 enrolled, nine were implanted with a mean follow-up of 14.9 months. It is noted that the efficacy results were not provided by the MAH. Regarding safety, of the 9 implanted patients, one discontinued long-term therapy after developing an infection at the pocket site and the central spinal fluid. Out of 15 patients 14 (93.3%) reported adverse events, 87 incidents in total. Most adverse events affected the digestive and nervous systems. Nausea, vomiting, hypotonia, convulsion and somnolence were among the most frequently reported adverse events.

Trial # D96-056: Surveillance program of Lioresal Intrathecal (baclofen injection) for cerebral origin spasticity

This was an observational study where the patients had pump refills at least every 90 days. Clinical evaluations at the visits included subject response to the drug (Ashworth Scale), adverse event and device complication assessment, and dosage requirements.

Patients included in this study were a subset of those who had participated in the clinical studies used to support the cerebral origin New Drug Application. In addition, they had to meet one of three secondary criteria to participate: 16 years or younger at time of implant, spasticity was a result of a brain injury, or one of the first ten subjects to enter the first controlled clinical trial.

Sixty-eight (68) patients between 4.0 and 36.0 years of age (median 12.0 years) were enrolled in phase one with diagnoses of spastic CP (n = 54), brain injury (n = 9), anoxia (n=3), transverse myelitis (n = 1), and degenerative brain disease (n = 1). Of the total of 68 subjects, 53 were under the age of 18 at implant.

The interpatient daily doses ranged from 15 to 1760 mcg/day throughout the surveillance period when analyzed at 3 month intervals. At three months after implant the average daily dose of patients for whom data were available was 156.6 mcg/day; the average daily dose nearly doubled at 24 months to 299.8 mcg/day.

During the 4,760 total months of follow-up, the average Ashworth scores for upper extremities have been maintained between 1.3 and 2.0 compared to the average baseline score for upper extremities of 2.3. The average Ashworth scores at follow-up for lower extremities ranged between 1.3 and 2.4. The average baseline score for lower extremities was 3.1.

During dose titration 34 patients experienced at least one of the 87 adverse events. In the maintenance phase, 34 patients experienced at least one of the 132 adverse events reported. In

total, 45 patients experienced at least one of the 219 adverse events over a follow up period of 4760.8 total months.

Two deaths occurred during the study: one patient, with a previous history of epilepsy, died of causes presumed to be related to a seizure and the other patient's death was attributed to upper airway obstruction associated with progression of Cerebral Palsy.

Out of the original 68 patients, 46 (68%) have experienced some type of device complication. 14 patients (21%) experienced both a procedure- and system-related complication. The complications were designated "procedure-related" if they occurred within 60 days after implant or were directly attributable to human intervention. Complications were "system-related" if they were attributable to the device whenever they occurred. The overall rate of device complications is approximately 2.8 per 100 patient months.

System-related complications accounted for 46 (42%) of the total 110 device complications; these occurred in 29 patients. 15 (33%) were related to the pump and 31 (67%) to the catheter. The majority of complications were procedure-related, accounting for 64 (58%) of the total 110 device complications; these occurred in 31 patients. Of these procedure-related complications, 3 (5%) were related directly to the pump and 9 (14%) were related directly to the intrathecal catheter.

The MAH concluded that Dosage requirements for children and adolescents do not seem to be different from that of adults. ITB delivered by the programmable SynchroMed Infusion System was found to be a safe and effective long-term treatment for patients with severe spasticity of cerebral origin.

Assessor's Comment

Upon closure of the Investigational New Drug (IND) clinical trials, the Post-Market Surveillance Program was developed to collect additional information on the long-term safety, efficacy, and dosing requirements of ITB. The provided final report encompasses data for each patient in the Surveillance Program, starting with their initial enrolment into the IND clinical trial from February 1989 to data received by Medtronic as of 31 July 2001, a span over twelve years. It is noted that the study enrolled a young population with 72% of the patients being less than 16 years of age and therefore provides important information, relevant to the use of ITB in the paediatric population. Furthermore it provides evidence of efficacy and safety for children with spasticity of cerebral origin older than 4 years of age. A limitation of the study is however the relatively small number of patients included (n=68). Efficacy of long-term Baclofen Intrathecal therapy is demonstrated by the maintenance of low Ashworth Scale scores. The average Ashworth scores (between 1.4 and 2.4 lower extremities and between 1.3 and 2.0 upper extremities) have been maintained for two years up to ten years of continuing ITB therapy. These results have been obtained with only moderate increases in average baclofen dose since early in follow-up. The study also provides valuable information on baclofen dosage in the paediatric population. The average daily dose at baseline was 84.4 mcg/day. Three months after pump implantation, the average dose of the patients was 156.6 mcg/day. The average daily dose nearly doubled at 24 months to 299.8 mcg/day, then became relatively stable. Regarding safety, most of the AEs were successfully managed by titration of the Baclofen dose.

Trial # D97-062: SynchroMed 10 ml pumps post-approval study

This was a multi-centre open-label study intended to collect data about the 10 ml SynchroMed pump in the paediatric population in actual clinical settings. The study was conducted in 11 centres in the US. The objectives of this Post-Approval Study were to monitor the performance of the pump in the paediatric population, monitor complications, and monitor events associated with growth and development over a one-year period, as requested by the FDA at the time of approval. This smaller SynchroMed model (10 ml vs. 18 ml reservoir volume) was developed for use in small (including pediatric) or thin patients whose body proportions would be unable to accept implantation of the larger 18 ml pump.

One hundred (100) patients with mean age 8.07 years (range 1.35-16.77 years) were enrolled in phase one. Patients had diagnoses of spastic CP (n = 90), Brain Injury (n = 5), near drowning (n=1), Anoxic (n = 3), Anoxic Encephalopathy (n = 1), Huntington's (n = 1) and Alobar Holoprosencephaly (n = 1). Ninety-two patients had data through 12 months and 5 patients were discontinued prematurely from the study due to device explant. Three patients were lost to follow-up. The average therapy follow-up time was 11.78 months (range 0.46-16.95 months).

The mean Ashworth Score change from baseline to 6 months was 0.72 and from baseline to 12 months was 0.75; both changes were statistically significant (p-values less than 0.001).

As was reported in previous annual reports, the clinical sites experienced significant difficulties in obtaining the required three serial measurements of height and/or weight. Because many patients with the diseases represented in this study had unusual postures due to their spasticity, or they were confined to a wheel chair, measuring height and weight was more difficult, and thus not done as routinely as in other paediatric populations.

There were a total of 142 adverse events experienced by 71 patients. Of these events, 48 were related to the system or implant procedure, 23 were related to intercurrent illness/injury/activity, 32 were due to underlying disease, and 29 were considered drug related. Four events were serious system-related complications, all associated with the catheter. Two of those events may have been caused by a non-standard combination of an intrathecal catheter and an EDM catheter.

In this study, there were 9 patients having a total of 11 infections. Most occurred within 2 months of implant or other invasive procedure. Six of the infections occurred among the 17 patients enrolled by one site, possibly related to a non-standard catheter configuration used by that site for some patients. Four of the 9 patients experiencing infections had their systems explanted, and were prematurely discontinued from the study. No data were available on prophylactic or peri-operative use of antibiotics. Patients included in the study had small body mass, possibly related to poor nutritional status. There was no evidence in this study of an association between infection and BMI.

There were 29 complications related to the pump implant site. These complications were more numerous among patients with low baseline BMI but at a statistical significance level. In only 2 of the 29 complications was there evidence to suggest a possible association with nutritional status or body size, and in only one of these cases did the investigator specifically mention nutritional status/size as a factor. There were 55 complications of types that could have potentially occurred as a result of patient growth. The majority of these occurred within 3 months of implant, during which little patient growth could be expected, especially in this population where growth appeared to be modest. Thus these would be not likely to have been caused by patient growth. For the 4 complications occurring 6 or more months after implant, association with patient growth is a possibility. However, in none of the cases did the investigator attribute the complication to patient growth.

Assessor's Comment

The rapporteur agrees with the conclusion of the MAH that in this study, the performance of the 10 ml pump in the paediatric population was adequate in both evidence of drug effect and delivery accuracy. The complications reported with the 10 ml pump are typical of those observed in other Medtronic studies. Infections were experienced by 9 of the 100 patients, resulting in system explant and discontinuation of therapy for 4 patients. While data are not complete on patient nutritional status and growth, the available data do not suggest that nutritional status or patient growth are important factors leading to complications in paediatric patients followed for one year after pump implant.

Pooled Results from Clinical Efficacy studies conducted in paediatric population relevant to target indication

As mentioned earlier, the data from studies VI, VIII, IX, X, XI, XII, and NVD94-043 were pooled and analyzed together. There were 253 patients enrolled in these studies, age 4 to 70.4 years (median 15.6 years), of whom 252 received study drug. The diagnoses included spastic CP (n=181), brain injury (n = 53), anoxia (n = 4), other cerebral origin (n = 12), and other (n = 3).

The long-term follow-up results included data from 188 patients implanted with the SynchroMed Infusion System. Thirty-four (34) patients discontinued the long-term follow-up.

Doses gradually increased in the first year after implant, but after 12 months doses remained relatively stable.

Adverse events were reported in 138 of the 252 subjects enrolled in the studies. There were a total of 562 adverse events reported over the duration of the study. There were 91 events that were considered serious including four deaths (due to motor vehicle accident – passenger, pneumonia, disseminated intravascular coagulation, respiratory/cardiac arrest). There were 5 withdrawal-associated events and 11 overdose-related events.

The pooled data from the studies noted above have been re-analyzed by age category to demonstrate safety and efficacy for paediatric use. Altogether, 154 paediatric patients were exposed to intrathecal baclofen, either in a trialling bolus or with chronic infusion, and 115 of these went on to have a permanent pump implanted for chronic infusion.

In some of the studies included in the pooled analysis, placebo-controlled cross-over studies of trialling boluses were used. Table A shows the number of responders to placebo or ITB, by bolus dose and by age category. Within each age and dose category, more subjects responded to baclofen than placebo, but small numbers in some combinations preclude statistically significant outcomes. It is important to note that the various studies were not well-standardized on how initial trialling doses were selected, or on escalation of dose upon either a positive or negative response. Trialling doses may not have been increased if an apparent drug-related adverse event was observed.

Table A: Comparisons of Response to ITB Bolus Trialling Doses vs Placebo Doses, by Bolus Dose and Age Category

25µg Baclofen Bolus Trialling Dose:

Placebo	Age 2-11 Baclofen		Age 12-17 Baclofen		Age 18+ Baclofen	
	NR	R	NR	R	NR	R
NR	8	8	8	5	5	2
R	1	3	0	6	0	1

p=0.039 p=0.063 p=0.500

50µg Baclofen Bolus Trialling Dose:

Placebo	Age 2-11 Baclofen		Age 12-17 Baclofen		Age 18+ Baclofen	
	NR	R	NR	R	NR	R
NR	8	38	9	13	10	9
R	5	3	4	0	0	3

p<0.001 p=0.049 p=0.004

100µg Baclofen Bolus Trialling Dose:

Placebo	Age 2-11 Baclofen		Age 12-17 Baclofen		Age 18+ Baclofen	
	NR	R	NR	R	NR	R
NR	2	4	4	2	4	5
R	0	2	1	2	1	0

p=0.125 p=1.000 p=0.219

Abbreviations: NR=No Response to Bolus, R=Response to Bolus, p=significance value for exact McNemar's test.

Because not all subjects were included in placebo-controlled crossover evaluations, trailing responses are also shown in Table B for all subjects who were trialled at one or more baclofen bolus doses. With the limitation noted earlier about variation in practice for starting and stopping of dose escalation, it appears that the paediatric age categories may have been more likely to respond to a 25µg bolus than adults. Response rates were fairly similar at higher doses.

Table B: Trialling ITB Dose and Response, by Study and Age Category

Trial Dose (µg)	Age 2-11 years		Age 11-17 years		Age 18+ years	
	N Tested	N Responded	N Tested	N Responded	N Tested	N Responded
25 – All Studies	23	13 (56.5%)	21	11 (52.4%)	8	3 (37.5%)
50 – All Studies	80	60 (75.0%)	46	26 (56.5%)	79	57 (72.2%)
75 – All Studies	9	7 (77.8%)	8	7 (87.5%)	19	14 (73.7%)
100 – All Studies	15	12 (80.0%)	17	10 (58.8%)	28	16 (57.1%)

Table C shows the number of adverse events associated with trialling bolus doses of ITB, by age and dose. Ignoring the 75µg bolus due to small numbers, the percent of subjects with adverse events tends to increase with dose for the paediatric categories, and not with adults.

Table C: Number of Adverse Events during ITB Trialling, by Dose and Age group

Trial Dose	Ages 2-11 Years				Ages 12-17 Years				Age 18+ Years			
	Number Trialed	Number of AEs	Number of Patients with AEs	%	Number Trialed	Number of AEs	Number of Patients with AEs	%	Number Trialed	Number of AEs	Number of Patients with AEs	%
25 µg	23	1	1	4.3%	21	2	2	9.5%	8	3	2	25.0%
50 µg	80	27	16	20.0%	46	4	3	6.5%	79	16	10	12.7%
75 µg	9	1	1	11.1%	8	5	2	25.0%	19	0	0	0.0%
100 µg	15	8	4	26.7%	17	8	6	35.3%	28	3	2	7.1%

Doses delivered to subjects during chronic dosing can be adjusted to effect and to avoid side effects, using the SynchroMed pump, and were not strictly dictated by the study protocols. Chronic doses varied widely over time. The biggest dose increases occurred within the first 12 months of treatment. Throughout chronic dosing, at least out to four years of dosing, the daily prescription of ITB tended to be lower for both paediatric age categories than for adults, and there was also a general trend toward lower average doses for the youngest age category.

Table D shows the median and inter-quartile (dose reported by 25-75% of patients) total daily dose range annually for patients by age group from these studies that supported the US NDA. This analysis removes the bias that may occur when evaluating mean dosing data that has large inter-patient variability, large standard deviations and a few patients reporting extremely large doses at the high end of dose ranges.

Table D: ITB doses ($\mu\text{g/day}$) at annual intervals by Age Group

Visit (Months)	Ages 2-11 Years				Ages 12-17 Years				Ages 18+ Years			
	n	Q1	Median	Q3	n	Q1	Median	Q3	n	Q1	Median	Q3
0	71	50.0	100.0	100.0	44	50.0	99.5	100.0	73	100.0	100.0	100.0
12	43	115.0	166.0	206.0	25	144.0	244.0	310.0	28	177.5	343.0	473.5
24	35	89.0	190.0	358.0	20	156.5	225.5	395.0	22	188.0	344.0	444.0
36	13	100.0	200.0	240.0	15	145.0	250.0	450.0	13	230.0	300.0	525.0
48	5	90.0	100.0	225.0	9	169.0	192.0	251.0	7	301.2	408.0	530.0

Q1=25th percentile; Q3=75th percentile (Q1-Q3 is interquartile range)

Assessor's Comment

The pooling of the results from studies conducted in USA to support the use of ITB provides some information relevant to the paediatric use; however due to limitations of the individual studies, the combined results should be reviewed with caution.

The number of patients included and analysed from these studies is presented below. The efficacy results demonstrated that chronic ITB infusion maintained patients at about a 1-point reduction in average Ashworth score in the lower extremities compared to that at baseline and similarly an average 1-point reduction in spasticity was seen in upper extremity Ashworth scores over time. The efficacy of treatment was generally maintained over time. It is noted however that the evaluation of patients was conducted in an open-label design and comparisons against placebo were limited.

Screening				Long-term		
Controlled studies						
Controlled studies	Enrolled	D/C after screening	Screened, not yet implanted	Implanted	D/C after implant	Active with pump
VI	82	28	0	54	17	37
XI	51	7	0	44	7	37
XIV	11	11	N/A	N/A	N/A	N/A
Total	144	46	0	98	24	74
Non-controlled physician trials						
VIII	5	1	0	4	1	3
IX	13	4	0	9	3	6
X	2	0	0	2	1	1
XII	4	3	0	1	0	1
Total	24	8	0	16	5	11
Treatment IND Protocol NVD94-043						
NVD94-043	89	6	9	74	5	69
Total	89	6	9	74	5	69
Grand total	257	60	9	188	34	154

Average daily dosing requirements were analyzed for all patients implanted with a pump receiving long-term treatment (N=188). In the first three months, dose increased by about 80% from 106 mcg/day to 191 mcg/day. Between 3 months and 1 year dose increased by about 44% from 191 mcg/day to 275 mcg/day; as mentioned by the MAH, after 1 year, doses remained relatively stable. In comparison to spinal spasticity, overall dose requirements were found to be lower in this paediatric cohort. This observation is based on data collected from 576 spinal spasticity patients implanted with pumps enrolled in the studies in the original NDA submission. Overall children under 12 years of age had an average daily dose of 274 mcg/day which was lower than both the 12 to 16 years and the over 16 years age groups. Daily doses were 384 mcg/day and 351 mcg/day respectively.

Regarding the reported AEs, The most frequent adverse events occurred in the nervous system, followed by the GI system. Nausea and vomiting were reported at a higher frequency during the initial phases of the studies. This may be due to the repeated lumbar punctures, especially in children.

The following serious adverse events were reported: Respiratory (11 cases), cardiovascular (4), withdrawal associated (5), meningitis/infection (17), death (4), seizures (29), overdose (11), and other (10). All patients except one (near drowning victim) had a previous history of seizures.

There were 185 device complications report in 99 patients. Of the 185 complications, 114 were procedure related. The most frequent procedure related complications were of the spinal site or track with 49 (25.8%), including CSF leaks, lumbar site infection, meningitis and spinal headaches. There were 71 system related complications (events occurring 60 days after implant and/or directly attributable to the device design or manufacturing). The most frequent system complications were those related to the catheter, including breaks, migrations, dislodgements and kinks.

1.2.2 Clinical Efficacy studies conducted in paediatric population with spasticity of spinal cord origin

Trial # D92-036: Surveillance program of Lioresal Intrathecal (baclofen injection) for spasticity of spinal cord origin

This was an observational study in which the subjects had pump refills at least every 90 days. Clinical evaluations at the visits included patients response to the drug (Ashworth and Spasm Scales), adverse event and device complication assessment, and dosage requirements. Patients were originally enrolled in one of the seven clinical trials that supported the original NDA.

Ninety-three (93) patients between 10 and 69 years of age (median 40 years) were enrolled in the surveillance program with diagnoses of Spinal Cord injury (n = 55), Multiple Sclerosis (n=36), and head injury (n= 2). It is noted in this study that only one patient was 10 year old at enrolment. During follow-up (8,046 total months), the average Ashworth scores were maintained between 1.1 and 2.0 while the average spasm score ranged between 0.3 and 1.2.

The interpatient daily doses ranged from 12 to 1920.3 mcg throughout the surveillance period. At three months after implant the average daily dose was 220.4 mcg/day; the average daily dose nearly doubled at 24 months to 414.3 mcg/day. The average daily doses became relatively stable after 24 months, varying 10% between 24 and 48 months.

There were a total of 552 adverse events experienced by 81 subjects during the surveillance period. Most commonly experienced events were hypotonia, somnolence, convulsions, dizziness, and constipation.

Fifteen (15) deaths occurred during the study, none of them were considered by the investigators to be related to ITB Therapy. Seven deaths were attributed to the natural progression of Multiple Sclerosis. Three deaths were attributed to pulmonary problems or pulmonary problems associated with genitourinary conditions. One death was attributed to a massive myocardial infarction, one to possible septic shock from urinary tract infection, one to suicide, one to a prior malignancy, and one to an unknown cause.

Assessor's Comment

This is an adult study in patients with spinal spasticity as only one child was enrolled. Therefore all the evidence could not easily extrapolated to the paediatric population. However, the rapporteur agrees with the MAH that the surveillance program provides evidence of safety and efficacy of long-term treatment of adult patients with spasticity of spinal cord origin. Furthermore it verifies previously reported findings of increasing average daily baclofen doses over the first two years of therapy followed by a relatively stabilization. Interestingly this study reports that 17.2% of the patients developed tolerance at an average of 21.5 months post-implant. In 80% of the time, "drug holidays" (baclofen weaned over a period of time and a new drug was temporarily introduced) were effective in that the baclofen therapy was re-introduced at a lower dosage.

1.2.3 Implantable Systems Performance Registry (ISPR) for ITB

The Implantable Systems Performance Registry (ISPR) is a web-based registry that was voluntarily created by the USA MAH to monitor the performance of products commercially available in the USA, specifically Medtronic intrathecal infusion and spinal cord stimulation systems. The ISPR was initially designed in August 2003 and collects data at 50 centres across the United States. Each ISPR centre follows its standard clinical practice for implanting infusion systems including patient selection, implant methods, and post implant therapy management. Patient and device information is collected for patients who were implanted prior to enrolment into the ISPR (existing patients) and prospectively for patients who were enrolled and followed since implant (new patients). After enrolment and initial data collection, all patients are followed prospectively for adverse events requiring surgical intervention or until the abandonment of therapy. Patient status updates were obtained every six months.

To be included in this analysis, patients had to be less than 18 years of age at the time of enrolment in the ISPR and implanted with an infusion system for treatment of intractable spasticity. The primary indication of intractable spasticity represents a group of movement related disorders associated with cerebral or spinal origin (e.g., cerebral palsy, multiple sclerosis, spinal cord injury, brain injury, or stroke).

A total of 276 paediatric patients were enrolled in the ISPR between August 7, 2003, and April 24, 2009. Approximately 60% of patients were children aged 2-11 years at enrolment and nearly 40% of patients were adolescents (ages 12-17 years). One infant (1-23 months) was enrolled in the ISPR. The majority of the paediatric patients in the ISPR being treated for intractable spasticity had either a sole sub-indication of cerebral palsy or cerebral palsy in combination with another sub-indication (79.0%, 218/276). Forty paediatric patients (14.5%) had an unknown or other sub-indication of intractable spasticity.

The average daily dose of baclofen at last follow-up visit for children was 393 mcg (SD = 325); the average daily dose for adolescents was 547 mcg (SD = 428) (n=263 paediatric patients).

The table below summarizes the baclofen daily dosage for paediatric patients for whom drug information was reported at the last follow-up visit.

Age Group	N	Daily Dose	
		Mean (Med) ± SD	(Min, Max)
Infant (<2y)	1	220.2 (220.2) ± NA	(220.2, 220.2)
Child (2-11y)	156	392.9 (290.4) ± 324.8	(0.1, 1599)
Adolescent (12-17y)	106	547.3 (459.6) ± 428.4	(0, 1717.1)

Note: Age group determined by age at enrollment.

Of the 276 paediatric patients in the ISPR, 43 were lost to follow-up (15.6%), 9 expired (3.3%), and 3 abandoned their infusion therapy (1.1%). These events are summarized below:

ISPR Event	Infant (<2y) N (%)	Child (2-11y) N (%)	Adolescent (12-17y) N (%)	Total N (%)
Patient Expired	0 (0.0%)	6 (3.6%)	3 (2.8%)	9 (3.3%)
Patient Lost to Follow-up	0 (0.0%)	21 (12.7%)	22 (20.2%)	43 (15.6%)
Therapy Abandoned	0 (0.0%)	3 (1.8%)	0 (0.0%)	3 (1.1%)
Total	1	166	109	276

Note: Age group determined by age at enrolment.

Of the 9 patient expired events, 1 (in a child) was attributed by the physician to an infection in the pump pocket; the remaining 8 patient expired events were determined to be unrelated to the implanted infusion system.

The average paediatric patient has been followed in the ISPR for 25 months since time of enrolment, with a range of 0 to 63 months of follow-up. Children and adolescents showed similar ranges of follow-up time as demonstrated below:

Age Group	N	Months from Implant		Months from Enrollment	
		Mean (Med) \pm SD	(Min, Max)	Mean (Med) \pm SD	(Min, Max)
Infant (<2y)	1	18.9 (18.9) \pm NA	(18.9, 18.9)	18.1 (18.1) \pm NA	(18.1, 18.1)
Child (2-11y)	168	36.4 (37.5) \pm 22.0	(0.5, 100.8)	25.0 (25.4) \pm 14.9	(0.0, 62.9)
Adolescent (12-17y)	109	38.1 (32.7) \pm 23.4	(1.6, 105.4)	24.4 (20.7) \pm 15.4	(0.0, 63.4)
Total	276	37.0 (34.8) \pm 22.5	(0.5, 105.4)	24.7 (23.2) \pm 15.0	(0.0, 63.4)

Note: *Months from Implant* is the number of months between the implant date of the first pump enrolled in the ISPR for that patient, and the last day that patient was considered active in the study (the event date, the center closure date, or the data cut-off date). The pump implant currently occurs prior to enrollment in the ISPR, meaning that in most cases, the patient had been implanted for some period of time before being enrolled in the ISPR.

Months from Enrollment is the number of months between the enrollment date of that patient's first pump in the ISPR, and the last day that patient was considered active in the study (the event date, the centre closure date, or the data cut-off date). Patients will have a minimum enrollment time of 0 months if the event date is before the pump enrollment date.

Assessor's Comment

The MAH correctly warrants that the ISPR was designed to collect data to evaluate and quantify survival for approved implantable system devices. The collection of infusion drug information is secondary to this objective, and because of this, the ISPR cannot supply detailed drug information at device implant, during titration of intrathecal drugs after therapy initiation, and throughout therapy maintenance. However, the ISPR provides a valuable snapshot of the average and wide range of doses determined by physicians to be sufficient for treatment of paediatric patients with intractable spasticity. Although the information is collected for a specific infusion device, the findings of this registry can be extrapolated in other certified implantable pumps utilised in MSs meeting the EU safety and health requirements.

IV.2 Overview of published literature of paediatric relevance

The literature review provided by the MAH has been conducted using the key search terms "paediatrics" and "baclofen". As a result of this search, 209 full text articles were reviewed. The dates of these articles span a 24 year period from 1985 until 2009. The focus of the literature search was to obtain ITB dosing information in the paediatric population and has been summarized by the MAH below:

2.1 Indication

The use of ITB appears to be increasing in patients with cerebral palsy (CP) over the last decade. CP patients suffer from severe spasticity and dystonia in varying degrees. The indications for treatment in the reviewed articles can be separated into a few main categories: dystonia, spasticity and cerebral palsy. There are 19 articles where the indication for treatment was mentioned as dystonia. There are a total of 90 articles where spasticity was mentioned (without dystonia reference) as indication for ITB treatment. This is spasticity of many origins including CP, cerebral origin, spinal origin, spinal cord injury, neurological disorders, brain injury, or MS. There are 23 articles in which CP was mentioned without reference to spasticity or dystonia. There are eight articles where spasticity and dystonia are both mentioned as the indication for treatment, i.e., a mixed patient population. As a conclusion in the majority of the articles spasticity was mentioned as the primary reason for ITB treatment.

2.2 Patient Population

The age of the children studied is included in a number of the reviewed articles. Often the age of the population cited included adults with a mean age in the paediatric range, less than 18 years of age. There tended to be large age ranges cited. It was rare to treat a child less than three

years of age with ITB, however there are only 3 articles that included one and two year olds. The lack of abdominal space for pump implant was often cited as the limitation for an ITB pump implant in the very young.

2.3 Screening or Test Dose

Screening or testing the patient's response to ITB prior to a pump implant is recommended in the majority of the articles. The method of testing appears to have evolved over the past decade based on experience gathered in the patient population. Earlier studies report use of a double-blind screen. More recently the majority of the articles report and recommend open-label screening with an escalating dose scheme; these articles are dated 2006 or later.

There are two defined types of screening; one for spasticity and another for the dystonia population. When the goal is to treat spasticity, single lumbar puncture screens are performed. The lumbar puncture screening doses are consistently reported in the following 25 µg increments: 25, 50, 75, and 100 µg. It is rare to screen with a single lumbar puncture above 100 µg but a 150 µg single lumbar puncture is cited in an article by Paret et al. The most common starting dose for screening is 50 µg with a 24 hour wait period prior to escalating to a single 75 µg dose, if unresponsive at 50 µg. If there is no response at 75 µg, escalation to a single lumbar puncture 100 µg dose can be administered 24 hours later. There are articles that report starting at 25 µg and escalating upwards, or even lower at 12.5 µg. Albright AL suggests starting at the 25 µg dose if the child is small or less than 40 lbs. Starting at 25 µg and escalating upwards in 25 µg increments is the second most common starting point for single lumbar puncture screen doses. Response at screening was consistently measured using the Ashworth scale. A meaningful clinical response was defined as either a one or two point drop in the Ashworth scoring when compared to baseline and measured every two hours through an eight hour interval following the single injection. The peak response to the single lumbar injection is reported at four hours post dose. Some articles cited a one or two point drop over two consecutive assessments as a meaningful clinical response

The screen for the dystonia patient population is with a continuous infusion This is thought to be necessary to achieve higher drug concentration, suggesting an intracranial site of action versus spinal. The screen is performed with an external infusion pump. The initial starting dose is most commonly reported as 200 µg/day. The dose is increased 50 µg every eight hours for a 48 to 72-hour period. Doses achieved prior to a response are much higher than a screen for spasticity, doses as high as 900 µg/day cited. The assessment tool most commonly used to measure response in the dystonia population is the Barry-Albright Dystonia scale (BAD). A clinically meaningful response is cited as a 25% reduction in score from baseline.

2.4 Initial Infusion Dosing

The initial infusion dose is the dose started in the hospital following the infusion pump implant. In the treatment of spasticity the most common starting dose is twice the lowest response dose in the screen. Given the most common starting dose in the screen for the treatment of spasticity is 50 µg, the initial starting dose following pump implant is most often reported as 100 µg/day.

The initial infusion dose in the treatment of dystonia is typically at 200 µg/day, the same as the initial screening dose. The dose is increased 50 to 100 µg/day.

2.5 Infusion Dosing in Follow-up

The majority of the articles that cited a follow-up period listed a period of one year or greater. The reports of how long it takes to obtain a stable ITB dose vary significantly from 6 months to up to 5 years. There are consistent reports cited in the literature that the longer the follow-up the more likely a stable dose is obtained for the patient. Stable doses as high as 1000 µg/day for ITB therapy are not uncommon with reports as high as 2000 µg/day. Higher stable doses are reported for spasticity of cerebral origin than of spinal origin. In addition, higher stable doses are reported for patients with dystonia than spasticity.

2.6 MAH's conclusions

It is evident from the literature that there is a lack of prospective controlled studies in the paediatric population with ITB. The patient populations were often not homogenous groups, adults and children were grouped together. In addition, the studies were often small and the cause of dystonia or spasticity had multiple origins. However, even with its limitations, the literature review did suggest a well supported screening procedure for patients with spasticity and dystonia with relative agreement to support a dosing procedure in both populations. There is a high inter-patient variability observed. The final dose level reached in the follow-up period appears to be affected by the degree of spasticity, the aetiology of the spasticity and weight and size of the child. The direct effect of each of these variables is unclear. However, the advantage of ITB therapy is the ability to titrate the dose to meet the needs of the patient.

Assessor's Comment

Overall the rapporteur agrees with the MAH regarding the evidence from the published literature. The limitations of the paediatric studies have been identified. However the evidence regarding the efficacy and safety of ITB use in the paediatric population is generally undisputable.

IV.3 MAH response to comments and recommendations in the Preliminary PdAR (Day 89)

3.1 MAH response to Rapporteur's comments and recommendations

The following rapporteur's comments and recommendations were addressed by the MAH in the response document:

Following the rapporteur's request, the MAH conducted a review of all Baclofen national SmPCs in the EU and has compiled the texts related to paediatric use of the drug from sections 4.1, section 4.2, section 4.4 and section 4.9. Reviewing the approved SmPCs, the MAH acknowledged that there are variations in the national texts across the EU. For the oral formulation, the MAH had updated the CDS (last CDS update dated 03 Jul 2008). However, the implementation of these proposed changes has varied across the member states which may in some part explain the variability in SmPC text. Regarding the Intrathecal formulation, which is registered in 14 EU MSs, the last update of the CDS was 07 September 2006. As with the oral formulations, there appears to be variability of implementation of the proposed text; the most detailed information on paediatric use appears in the UK and French SmPCs.

Assessor's Comment

The MAH as requested has provided a comprehensive overview of the variations in the national SmPC regarding the use of the oral and the IT Baclofen formulations. The rapporteur concluded in the preliminary PdAR that this is not optimal as the use of Baclofen represents a very common clinical paediatric practice which should be standardized for all member states. This is the aim of this European work-sharing procedure under Article 45.

In the preliminary PdAR the rapporteur questioned the availability of the evidence regarding the paediatric use of Baclofen in conditions other than the spasticity of cerebral origin. This comment was not endorsed by the Netherlands which stated that "extrapolation of the adult efficacy to all conditions that result in muscular spasms in children is considered acceptable." The MAH states that all the provided data support that Baclofen will be effective in the treatment of any condition associated with muscle spasticity in the paediatric population, with a similar mode of action as in adults.

Assessor's Comment

The rapporteur argues with the conclusion that the mechanism of Baclofen treatment (interruption of the spinal reflex that induces spasticity) is similar in paediatric and in adult patients. However from the clinical studies and the evidence submitted by the MAH, there is no information available on the positive effect of the Baclofen treatment in paediatric patients with spasticity of spinal origin. The symptomatic treatment of the spasms should facilitate the individual needs of the patients, whether that means preservation of muscle tone for ambulation or increases muscle relaxation for ease of care; these are often different between patients with CP and spinal disorders. It is noted that in the only spinal spasticity study provided by the MAH (Trial #D92-036) only one paediatric patient was included.

Regarding the variation in the posology for the Baclofen oral formulation in the paediatric population, the MAH argues the proposed regime reflects the needed flexibility in order to accommodate the high inter-patient variability of the treatment response. The selection of the initial dose, the titration procedure and the duration of treatment, although it is based on evidence reflected in section 4.2 of the SmPC, it can be individualized based on the expected outcomes for the individual patients. The MAH concludes that "in our opinion appears to be flexible enough to allow individualised patient treatment in terms of variability to treatment response, while providing the framework for clinicians that provides them with clear information and instruction on optimal administration of the drug."

Assessor's Comment

The rapporteur agrees with the MAH that a level of flexibility is needed in order to individualize the treatment, based on the accepted therapeutic outcome for the patient. This mode of prescribing is expected to increase adherence to treatment by limiting the undesirable AEs which often influence tolerability of Baclofen. However as mentioned before, the proposed dosing regimes in the SmPCs/PILs should be standardized across the EU MSs in the best way which reflects the current clinical evidence of optimal treatment with Baclofen.

As the use of ITB appears to be significantly in Europe, although in certain instances unlicensed, the MAH was requested to summarise all available paediatric information which should be included in appropriate sections of the SmPCs/PILs. The MAH provided significant additional information from the 11 studies conducted in USA, from the review of the published literature and the utilization of experts in the field. Overall it is concluded that all of the data sources demonstrate the inter-patient variability of ITB dosing and also show that the dose tends to increase with chronic dosing. It is evident from the literature that the currently available studies have significant limitations such as lack of prospective controlled design, small number of patients without homogeneity of the diagnosis, adult and paediatric results often analyzed collectively. Furthermore, the MAH states that the clinical studies and post-marketing registry data presented in this report provide more data supporting dosing for children 4 years of age and older and therefore ITB therapy for patients 2-4 years of age should be undertaken with care and the decision to administer the therapy needs to be based upon the treating physician's consideration of individual benefit and risk for each patient.

Similarly although the data supporting spinal origin spasticity is limited from the clinical studies, postmarketing surveillance and the post-market implantable product registry, the presumed mechanism of action should be the same for cerebral or spinal origin spasticity. The available data all support the safety and efficacy of ITB for paediatric patients when administered by expert physicians.

Assessor's Comment

The rapporteur agrees that the MAH has provided a comprehensive overview of all available information regarding the paediatric use of ITB, by utilizing different sources of data. The

limitations of the available evidence are acknowledged; however it accepted that the use of ITB in children is widespread. Keeping in mind the individuality of patients with spasticity, every effort should be made to promote the evidence-based management of these patients. The rapporteur confirms that by reviewing the provided information, appropriately harmonized paediatric text for SmPC/PIL should be included in all Baclofen containing products (oral formulations and IT) in Europe. Also see comments in section.....

Finally the rapporteur proposed that “the MAH could explore this opportunity for proactive collection of data relating to the paediatric use of this drug, including dosing protocols, safety and effectiveness, through setting up a registry”. As a response the MAH agreed that collecting ongoing data related to paediatric use of baclofen is desirable. Such a registry appears to be available in USA, the Implantable Systems Performance Registry (ISPR), voluntarily created by Medtronic. Data generated in the ISPR Registry were included and analysed as part of this ongoing work-sharing procedure. However the MAH states that there are currently no plans to initiate a European post-market paediatric registry. Medtronic continues to conduct the Implantable Systems Performance Registry in the United States and will continue to submit annual update reports to the United States Food and Drug Administration. The MAH concludes that the report can also be made available to European Health Authorities.

Assessor’s Comment

The existence of a registry in USA associated with the use of ITB in the paediatric population is welcomed. However as stated by the MAH the registry is design to collect information on the performance of the approved implantable system devices; therefore the ISPR cannot supply robust information on the safety and efficacy of the ITB due to the lack of detailed drug information collected. The rapporteur strong recommends that Medtronic should consider extending the objectives of this already established ISPR registry to collect important and needed data on dosage, effectiveness, safety and tolerability not only on the delivering device but also on the drug itself. The MAH’s proposal for the data from the ISPR registry to become available in Europe as well is endorsed. However the rapporteur considers the lack of initiative in developing a European registry for the paediatric ITB disappointing as the collection of paediatric data is not only desirable, it is considered essential.

3.2 MAH response to comments and recommendations from other MSs

With regards to the justification of the recommended oral dosage scheme as requested by one MS, the MAH states that therapeutic blood levels of baclofen have been described in the current MAH CDS, which states that Baclofen is rapidly and completely absorbed from the gastrointestinal tract. No significant difference between syrup and tablet formulation is observed in respect of t_{max}, C_{max}, and bioavailability. Following oral administration of single doses of 10, 20, and 30 mg baclofen, peak plasma concentrations averaging about 180, 340, and 650 ng/mL, respectively, are recorded after 0.5 to 1.5 hours. The corresponding areas under the serum concentration curves (AUCs) are proportional to the size of the dose.

Regarding the comments from another MS, the MAH concurs with the view that the efficacy data for baclofen of adults can be extrapolated to children and hence a restricted indication is not justified. The MAH response to the above comments was included in the proposed wording of the relevant sections of the SmPC/PIL.

3.3 MAH proposed SmPC/PIL wording

3.3.1 Proposed SmPC wording for section 4.1 and 4.2 for Baclofen 5 mg, 10 mg and 25 mg tablets, 1 mg/mL syrup

Section 4.1 Therapeutic indications

Children

Spasticity of the skeletal muscles in multiple sclerosis. Spastic conditions occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin: e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasm of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

Section 4.2 Posology and method of administration

Children

Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), preferably in 2-4 divided doses. Therefore, Baclofen tablets are not suitable for use in children below 33 kg body weight.

The dosage should be raised cautiously, at about 1 to 2 week intervals, until it becomes sufficient for the child's individual requirements. The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

3.3.2 Proposed PIL paediatric wording for Baclofen 5 mg, 10 mg and 25 mg tablets, 1 mg/mL Syrup

2. Before you take Baclofen tablets syrup

- Use in children and adolescents

Baclofen tablets are not suitable for use in children below 33 kg body weight.

3. How to take Baclofen tablets in children and adolescents

Children's treatment is adjusted to their weight. Baclofen tablets are not suitable for use in children below 33 kg body weight.

The dose prescribed by your doctor may be different from that written here. If this is the case, follow the doctor's instructions.

Your doctor will tell you exactly how many tablets or mL of Baclofen to take.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

3.3.3 Proposed SmPC wording for section 4.1 ; 4.2; 4.4 for Baclofen Intrathecal

Section 4.1 Therapeutic indications

Children

Baclofen Intrathecal is indicated in patients with severe chronic spasticity of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) or of cerebral origin who are unresponsive to orally administered antispastics (including oral Baclofen) and/or who experience unacceptable side effects at effective oral doses.

For patients with spasticity due to head injury, it is recommended not to proceed to long-term Baclofen Intrathecal therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury). A small number of patients with tetanus have been successfully treated with Baclofen Intrathecal to reduce hyperreflexia, clonus, and trismus.

Section 4.2 Posology and method of administration

Children

[Note: The general information regarding posology currently included in the Baclofen IT CDS should remain intact. The below proposal relates to specific paediatric dosing language elaborated below.]

Screening phase

The initial lumbar puncture trailing dose for patients 2-11 years of age and 11-17 years of age should be 25-75 µg/day based upon age and size of the child. Initial trialling doses greater than 25 µg should be considered based upon the age and size of the paediatric patient. The most commonly reported initial trial dose associated with a response is 50 µg/day. Patients who do not experience a response may receive a 25 µg/day dose escalation every 24 hours. The maximum trialling dose should not exceed 100 µg/day in paediatric patients.

Dose Titration phase

No proposed changes

Maintenance Therapy

In children with spasticity of cerebral and spinal origin, the maintenance dosage for long-term continuous infusion of Baclofen Intrathecal ranges from 87.3 ± 29 µg/day (range of 35.0 – 195.0 µg/day) for patients 4-11 years and 84.8 ± 30.7 µg/day (range of 50.0 -200.0 µg/day) for patients 12-17 years of age.

There is limited experience with doses greater than 1,000 micrograms/day.

Section 4.4 Special Warnings and Precautions for use

There is very limited clinical data on the use of Baclofen Intrathecal in children under the age of four years. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.

Assessor's Comment

Regarding the proposed wording in the SmPC/PIL of the oral and IT formulations of Baclofen and taking into account comments received from CMSs after the circulation of draft final PdAR (Day 90), the rapporteur has the following comments (Please see proposed wording in section V of this assessment report):

- Regarding the paediatric indications of Baclofen regardless of the formulation, it is considered that the principal indication for which the majority of evidence of the positive effect of the symptomatic treatment with Baclofen exists is the spasticity of cerebral origin; the rapporteur is of the view that this should be clearly demonstrated in the wording in section 4.1. Overall it is accepted that Baclofen could be used for the symptomatic treatment of all conditions which lead to central motor neuron spasticity. It has been argued that listing these conditions in section 4.1 of the SmPC might not be optimal: "By mentioning too many examples, there is a suggestion of completeness. Furthermore, it is implicitly suggested that only spasticity caused by these diseases may be treated." (comments from NL on the day 90 report). The rapporteur considers that the wording in section 4.1 should reflect the majority of the conditions for which Baclofen is expected to be beneficial in order to facilitate all prescribers in identifying the patients which should receive this treatment. A small amendment to the wording has been done to better reflect the fact that this list is not exclusive.
- Based on comments received from CMSs (NL and DE) following the circulation of day 90 PdAR, the rapporteur concludes that the wording regarding the use of Baclofen in spasticity due to head injury should be removed from section 4.2 and should be included in section 4.4-Special warnings and precautions for use.

- Regarding the posology of the oral formulations of Baclofen, the rapporteur agrees with the recommended starting and maintenance doses. These should be preferably administered in 4 divided doses in order to limit the risk of undesirable effects. The titration of the dose until the desirable clinical effect should be at 1 week intervals, a period sufficient long to review response and minimize time of the patient in an ineffective dose.
- Regarding the paediatric use of ITB, the MAH does not propose an age limit to its use. This view has been further supported by NL in comments received following the circulation of the Day 90 PdAR. However, it is recognized that very little data on intrathecal baclofen use is available under the age of 4 years. In the new clinical studies submitted, the lack of evidence regarding the dosing and the safety profile of ITB in children younger than 4 years has been highlighted. It is recognized that in specialized centres, there might be significant experience in treating very young children with spastic conditions as these patients could benefit from baclofen. However even in the published literature, the evidence is inconclusive as problems have been identified with the implantable pump or the drug in very young children, particularly with low body mass. The rapporteur concludes that due to lack of evidence on the safety and efficacy, the use of ITB should not be recommended below 4 years of age. This view has been supported by comments received from other CMSs (IR, DE and SE). It is however recognized that there is and continue to be some off-licensed use of ITB in those rare cases of very young patients where specialized clinicians will individually assess the risk:benefit of the drug.
- The rapporteur agrees with the proposed dosing regime of 25-75 µg/day based upon age and size of the child. The evidence supports the view that most commonly reported initial trial dose associated with a response is 50 µg/day. Patients who do not experience a response may receive a 25 µg/day dose escalation every 24 hrs, but should not exceed 100 µg/day. The rapporteur proposes the inclusion of the following phrase in section 4.2 “The total daily dose tends to increase over the first year of therapy, therefore the accurate maintenance dose needs to be adjusted based on individual clinical response.”

V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATIONS ON DAY 120

Based on the evidence submitted by the MAH and Medtronic, the rapporteur concludes that the data justified the use of oral formulations of Baclofen (tablets and syrup) in the entire paediatric population as symptomatic treatment of spasticity. The rapporteur agrees with the MAH that the dosing regimes in the SmPCs/PILs should be standardized across the EU MSs in the best way which reflects the current clinical evidence of optimal treatment with Baclofen.

Regarding the paediatric use of intrathecal Baclofen the rapporteur concludes that the provide evidence support the extension of the use of ITB in patients older than 4 years of age. For children younger than 4 years of age the use of ITB is not recommended due to insufficient data on safety and efficacy. It is noted that in all the paediatric clinical studies provided by the MAH, a single type of implantable pump has been utilized. The rapporteur concludes that the safety and efficacy evidence on the paediatric use of ITB has been considered regardless of the device used; there is no evidence to suggest that the use of other EU certified pumps would lead to different therapeutic effect of Baclofen if implemented and monitored by physicians trained in chronic intrathecal infusion therapy.

The rapporteur reviewed the MAH’s proposals and concluded that the changes in the SmPC and PIL of Baclofen containing products (oral and IT formulations) should comprehensively reflect the available paediatric information.

Based on the review of the presented paediatric data the rapporteur considered that:
For all products containing Baclofen across the EU, it is recommended that SmPCs and PILs contain the following statements;

Proposed SmPC wording for tablets (5 mg, 10 mg and 25 mg) and oral syrup (1 mg/mL) Baclofen

Section 4.1 Therapeutic indications

Paediatric population (0-18 years)

Baclofen is indicated for the symptomatic treatment of spasticity of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

Baclofen is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

Section 4.2 Posology and method of administration

Paediatric population (0-18 years)

Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), preferably in 4 divided doses.

The dosage should be raised cautiously, at about 1 week intervals, until it becomes sufficient for the child's individual requirements. The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

Baclofen tablets are not suitable for use in children below 33 kg body weight.

Section 4.4 Special Warnings and Precautions for use

There is very limited clinical data on the use of Baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.

Proposed SmPC wording for Baclofen Intrathecal

Section 4.1 Therapeutic indications

Paediatric population

Baclofen Intrathecal is indicated in patients aged 4 years and above with severe chronic spasticity of cerebral origin or of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) who are unresponsive to orally administered antispastics (including oral Baclofen) and/or who experience unacceptable side effects at effective oral doses.

Section 4.2 Posology and method of administration

Baclofen Intrathecal is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, in implantable pumps suitable for continuous administration of Baclofen Intrathecal into the intrathecal space (EU certified pumps). Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with intrathecal bolus, followed by a very careful individual dose titration prior to maintenance therapy. Intrathecal administration of Baclofen through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience. Specific instructions for implantation, programming and/or refilling of the implantable pump are given by the pump manufacturers, and must be strictly adhered to.

Paediatric population

Screening phase

The initial lumbar puncture test dose for patients 4-18 years of age should be 25-50 µg/day based upon age and size of the child. Patients who do not experience a response may receive a 25 µg/day dose escalation every 24 hours. The maximum trialling dose should not exceed 100 µg/day in paediatric patients.

Dose Titration phase

No proposed changes

Maintenance Therapy

The clinical goal is to maintain as normal a muscle tone as possible, and to minimise the frequency and severity of spasms without inducing intolerable side effects. The lowest dose producing an adequate response should be used. The retention of some spasticity is desirable to avoid a sensation of “paralysis” on the part of the patient. In addition, a degree of muscle tone and occasional spasms may help support circulatory function and possibly prevent the formation of deep vein thrombosis.

In children with spasticity of cerebral and spinal origin, the maintenance dosage for long-term continuous infusion of baclofen Intrathecal ranges from 87.3 ± 29 µg/day (range of 35.0 – 195.0 µg/day) for patients 2-11 years and 84.8 ± 30.7 µg/day (range of 50.0 -200.0 µg/day) for patients 12-17 years of age.

There is limited experience with doses greater than 1,000 micrograms/day.

The total daily dose tends to increase over the first year of therapy, therefore the accurate maintenance dose needs to be adjusted based on individual clinical response.

Section 4.4 Special Warnings and Precautions for use

For patients with spasticity due to head injury, it is recommended not to proceed to long-term Baclofen intrathecal therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Use of intrathecal Baclofen in the paediatric population should be only prescribed by medical specialists with the necessary knowledge and experience. There is very limited clinical data regarding the safety and efficacy of the use of baclofen Intrathecal in children under the age of four years.

VI. SUPPLEMENTARY INFORMATION AND ASSESSMENT

In June 2010 the MAH identified some remaining issues regarding the proposed wording recommendations for both the oral liquid formulation of Baclofen and the ITB. The majority of the issues raised were minor such as definition of the paediatric age groups; in addition the MAH raised 2 issues regarding the dosing regimes for the oral formulations and the intrathecal administration of Baclofen. Following discussions with the rapporteur, the MAH was requested to submit supporting information to justify the proposed changes for the information included in section 4.2 of the SmPC.

For the oral administration of Baclofen, the MAH questioned whether the division of the total dose in 4 doses per day was feasible due to the variable availability of the liquid formulation across Europe. Although concerns were raised by the rapporteur regarding the accurate titration of the paediatric dosing regime, it was accepted that the wording should reflect the formulations currently available. Furthermore the MAH expressed the intention to further investigate the availability of age appropriate formulation (liquid) in all member states which is strongly supported by the rapporteur.

Regarding ITB, following the circulation of Baclofen Final PdAR, the MAH reviewed the evidence regarding the proposed dosing regime for children older than 4 years during Maintenance Therapy and proposed changes in the already agreed wording for section 4.2. The rapporteur supported the view that the dosing regimes in the SmPCs should be standardized across the EU MSs in the best way which reflects the current clinical evidence of optimal treatment with intrathecal Baclofen. The additional information provided by the MAH was reviewed and a supplementary assessment report was circulated to MSs for comments. The overall conclusions of the Rapporteur regarding the finalized wording included in the SmPCs and PIL of all products containing Baclofen across the EU were fully endorsed.

VII. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Based on the review of the presented paediatric data the rapporteur considers that for all products containing Baclofen across the EU, it is recommended that SmPCs and PILs contain the following statements:

Proposed SmPC wording for Baclofen 5 mg, 10 mg and 25 mg tablets, 1 mg/mL syrup

Section 4.1 Therapeutic indications

Paediatric population

Baclofen is indicated in patients 0 to <18 years for the symptomatic treatment of spasticity of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

Baclofen is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

Section 4.2 Posology and method of administration

Paediatric population (0 to <18 years)

Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), in 2-4 divided doses (preferably in 4 divided doses).

The dosage should be raised cautiously, at about 1 week intervals, until it becomes sufficient for the child's individual requirements. The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

Baclofen tablets are not suitable for use in children below 33 kg body weight.

Section 4.4 Special Warnings and Precautions for use

There is very limited clinical data on the use of Baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.

Proposed PIL wording for Baclofen 5 mg, 10 mg and 25 mg tablets, 1 mg/mL syrup

Please read this product information carefully before you or your child is given Baclofen since it contains important information

1. What Baclofen is and what it is used for

Your doctor has decided that you or your child needs this medicine to help treat your condition.

Baclofen is used to reduce and relieve the excessive tension in your muscles (spasms) occurring in various illnesses such as cerebral palsy, multiple sclerosis, cerebrovascular accidents, spinal cord diseases and other nervous system disorders.

2. Before you take Baclofen

Children and adolescents:

Baclofen tablets are not suitable for use in children under 33 kg body weight.

3. How to take Baclofen

Use in children (0 to <18 years)

Children's treatment is adjusted to their body weight. Children's treatment usually starts with a very low dose (approximately 0.3 mg/kg/day), in 2-4 divided doses (preferably in 4 doses). The dosage then gradually increased until it becomes sufficient for the child's individual requirements, this may be between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given. Baclofen tablets are not suitable for use in children below 33 kg body weight.

Proposed SmPC wording for Baclofen Intrathecal

Section 4.1 Therapeutic indications

Paediatric population

Baclofen Intrathecal is indicated in patients aged 4 to <18 years with severe chronic spasticity of cerebral origin or of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) who are unresponsive to orally administered antispastics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses.

Section 4.2 Posology and method of administration

Baclofen Intrathecal is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, in implantable pumps suitable for continuous administration of Baclofen Intrathecal into the intrathecal space (EU certified pumps). Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with intrathecal bolus, followed by a very careful individual dose titration prior to maintenance therapy. Intrathecal administration of Baclofen through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience. Specific instructions for implantation, programming and/or refilling of the implantable pump are given by the pump manufacturers, and must be strictly adhered to.

Paediatric population

Screening phase

The initial lumbar puncture test dose for patients 4 to <18 years of age should be 25-50 µg/day based upon age and size of the child. Patients who do not experience a response may receive a 25 µg/day dose escalation every 24 hours. The maximum screening dose should not exceed 100 µg/day in paediatric patients.

Dose Titration phase

No proposed changes

Maintenance Therapy

The clinical goal is to maintain as normal a muscle tone as possible, and to minimise the frequency and severity of spasms without inducing intolerable side effects. The lowest dose producing an adequate response should be used. The retention of some spasticity is desirable to avoid a sensation of “paralysis” on the part of the patient. In addition, a degree of muscle tone and occasional spasms may help support circulatory function and possibly prevent the formation of deep vein thrombosis.

Paediatric population

In children aged 4 to <18 years with spasticity of cerebral and spinal origin, the initial maintenance dosage for long-term continuous infusion of Baclofen Intrathecal ranges from 25 to 200 mcg/day (median dose: 100 mcg/day). The total daily dose tends to increase over the first year of therapy, therefore the maintenance dose needs to be adjusted based on individual clinical response. There is limited experience with doses greater than 1,000 micrograms/day.

The safety and efficacy of Intrathecal Baclofen for the treatment of severe spasticity of cerebral or spinal origin in children younger than 4 years of age have not been established (also see section 4.4).

Section 4.4 Special Warnings and Precautions for use

For patients with spasticity due to head injury, it is recommended not to proceed to long-term Baclofen intrathecal therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Use of intrathecal Baclofen in the paediatric population should be only prescribed by medical specialists with the necessary knowledge and experience. There is very limited clinical data regarding the safety and efficacy of the use of Baclofen Intrathecal in children under the age of four years.

Proposed PIL wording for Baclofen Intrathecal

Please read this product information carefully before you or your child is given Baclofen Intrathecal since it contains important information.

1. What Baclofen and what is it used for

Your doctor has decided that you or your child needs this medicine to help treat your condition. Baclofen Intrathecal is intended for adults and children of 4 years and above and is used to reduce and relieve the excessive tension in your muscles (spasms) occurring in various illnesses such as cerebral palsy, multiple sclerosis, spinal cord diseases, cerebrovascular accidents, and other nervous system disorders.

2. Before you take Baclofen

Children and adolescents:

Baclofen intrathecal formulation is intended for children of 4 years and above.

The applicant was requested to submit a Type IB C.1.3 variation to update the SmPCs and PILs of products containing the active ingredient Baclofen (oral and intrathecal formulations) in line with the above work-sharing recommendations within 90 days of this report.

VIII. MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED ADDITIONAL INFORMATION REQUESTED

LIORESAL

Intrathecal Injection 50mcg/1ml, Infusion 10mg/20ml or Infusion 10mg/5ml

Oral solution 5mg/5ml

Tablets 10mg

Marketing Authorisation Holder: