HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

10 May 2006

InductOs 12 mg, kit for implant
Box of 1
CIP code: 564 511-5

Applicant: Wyeth Pharmaceuticals

dibotermin alfa

List I
Drug for hospital use only. May only be prescribed by specialists in orthopaedic surgery (traumatology)

Date of marketing authorisation : 09 September 2002

Date of amendment to marketing authorisation: 29 March 2005 (extension of indications)

Reason for request: inclusion on the list of medicines approved for use by hospitals in the indication “substitute for autogenous bone graft for single-level (L4-S1) anterior lumbar spine fusion in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition”.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Dibotermin alfa

1.2. Indications

InductOs is indicated for single-level (L4 – S1) anterior lumbar spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition.

InductOs is indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.

1.3. Dosage

InductOs should be used by an appropriately qualified surgeon.

InductOs is prepared immediately prior to use from a kit containing all necessary components. Once prepared, InductOs contains dibotermin alfa at a concentration of 1.5 mg/mL (12 mg per kit).

InductOs should not be used in concentrations higher than 1.5 mg/ml (see section 4.9 Overdose)

There is very limited experience of the efficacy and safety of InductOs in the elderly (> 65 years of age).

The efficacy and safety of InductOs in children and newborns has not been established.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2005 classification

M : musculo-skeletal system
M05 : drugs for treatment of bone diseases
M05B : drugs affecting bone structure and mineralisation
M05BC : bone morphogenetic proteins
M05BC01 : BMP-2

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

None
No other medicines with marketing authorisation are available in this indication.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy and undesirable effects

Open, randomised study of 279 patients aged 19–78 years with symptomatic lumbar disc degeneration for at least six months who had not responded to non-operative treatment and who were undergoing open anterior lumbar interbody fusion with the LT-CAGE Lumber Tapered Fusion Device filled with either InductOs (n=143) or autogenous bone graft taken from the iliac crest (n=136).

Variables relating to the surgical procedure

	InductOs (n=143)	Control group (n=136)	p
Mean duration of surgical procedure (hours)	1.6	2	<0.001
Mean length of hospital stay (days)	3.1	3.3	NS
Mean blood loss (ml)	109.8	153.1	0.016

A single, multi-component endpoint was used: overall success. It consists of the following primary efficacy and safety considerations:

1. Radiologically demonstrated fusion
2. Oswestry pain/disability improvement
3. Maintenance or improvement in neurological status
4. No undesirable events
5. No additional surgical procedure performed that was classified as a “failure”.

Results

- *Efficacy*

At 24 months post-operation, InductOs was demonstrated to be statistically non-inferior to autogenous bone graft.

Overall success rate was 57.5% versus 55.8% (95% two-sided CI of the difference: -10.72, 14.01) for InductOs and autogenous bone graft respectively.

The success rate for radiologically determined fusion was 94.4% versus 88.9% for InductOs and autogenous bone graft respectively (95% two-sided CI of the difference: - 1.53, 12.46).

For pain and disability (Oswestry score) the success rate was 72.9% versus 72.5% for InductOs and autogenous bone graft respectively (95% two-sided CI of the difference: - 11.2, 12.0).

- *Undesirable effects*

The undesirable effects were similar in both groups. The most common undesirable effects were accidental injury, neuralgia, back pain and bone disorder (spontaneous fractures).

3.2. Conclusion

An open trial demonstrated that at one year InductOs was not inferior to autogenous bone graft in patients with symptomatic degeneration of the lumbar discs. However, the efficacy of lumbar spine fusion in back pain associated with degenerative lesions is disputed.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

- Chronic low back pain associated with degenerative disc disease can result in reduced functional capacity.
- InductOs is a symptomatic treatment.
- In view of the results of the clinical trial showing that InductOs was not inferior to autogenous bone graft, the Committee considered that, in cases where there are sound reasons for performing lumbar spine fusion, the ratio of efficacy to undesirable effects for InductOs was high.
- InductOs provides a substitute for autogenous bone graft in the indication of lumbar spine fusion in adults who have had at least 6 months of non-operative treatment in the indication of lumbar spine fusion.
- However, at present, the efficacy of spine fusion techniques in managing chronic back pain associated with degenerative disc disease is disputed.
- Benefit to public health
  - In terms of public health the burden represented by chronic low back pain associated with degenerative disc disease requiring spine fusion cannot be quantified. It is small at most because of the limited number of patients affected.
  - A public health need does exist in chronic low back pain which is inadequately met. However, management of chronic low back pain associated with degenerative disc disease requiring spine fusion does not represent a public health need.
  - In view of the trial results and given the available alternatives, this medicinal product is not expected to have any impact in terms of reducing morbidity.
  - In conclusion, in view of the available data, no benefit to public health is expected for the medicinal product InductOs.

The Actual Benefit from InductOs in this indication is moderate.

4.2. Improvement in Actual Benefit

InductOs provides no Improvement in Actual Benefit (level V) compared to autogenous bone graft for anterior lumbar spine fusion in adults with degenerative disc disease.

4.3. Therapeutic use

Management of low back pain involves identifying its cause and its risk factors. This forms the basis oftherapy.

Physical treatment based on re-education (stretching exercises, building muscle strength, stabilising the spine, developing cardiorespiratory fitness) combined with cognitive and behavioural management are the cornerstones of treating chronic low back pain. Analgesics (NSAIDs or others) can be useful.

Spinal fusion may be considered for non-surgical treatment failures followed up for at least two years. Its aim is to achieve union between two or more lumbar vertebrae.

A randomised trial performed in 294 selected patients with chronic low back pain associated with degenerative disc disease demonstrated that this fusion technique was superior to non-surgical treatment.[1]

However, a literature review carried out by ANAES in 2000[2] found that the methodological quality of the available trials was poor and concluded that: “In isolated low back pain, there is no evidence for the efficacy of arthrodesis compared with another form of treatment, which could be either medical or surgical (particularly disc protheses)”.

In addition a recent Cochrane review[3] found no grounds for concluding that spinal fusion was an effective treatment for degenerative disc disease.

The efficacy of lumbar spine fusionthus remains controversial in treating chronic low back pain and there is no consensus about its indications.

It appears, however, that this technique is of real benefit to patients in certain circumstances, which need to be better defined[2].

In cases where there are grounds for performing lumbar spine fusion, InductOs offers an alternative to autogenous bone graft.

No data is available which demonstrate that InductOs reduces the risk of non-union.

4.4. Target population

The target population for InductOs is defined as those patients with chronic low back pain associated with degenerative disc disease who are likely to be treated with lumbar spine fusion.

No epidemiological data is available about lumbar spine fusion in France.

According to ANAES, 30 481 lumbar spine procedures were performed in France in 1998 including 1,827 spine fusions.

On the assumption that the number of lumbar spine fusions increased by 10% between 1998 and 2006, approximately 2,000 lumbar spine fusions would have been performed in France in 2006.

As a result the target population for InductOs is between 1,500 and 2,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services in the new indication and at the posology in the marketing authorisation.

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[1] Fritzell et al. 2001 Volvo award winner in clinical studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine 2001;26:2521-32.

[2] ANAES Guidelines 2000. Disc prostheses and arthrodesis in degenerative disease of the lumbar spine.

[3] Gibson and al. Surgery for degenerative lumbar spondylosis: updated Cochrane Review. Spine 2005;30:2312-20.