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TRANSPARENCY COMMITTEE

Opinion
1st October 2014

BEROMUN 1 mg/5 ml, powder and solvent for solution for infusion
B/1 (CIP: 34009 561 657 9 7)

Applicant: Boehringer Ingelheim France

INN	Tasonermin
ATC code (2013)	L03AX11 (cytokines and immunomodulators)
Reason for the request	**Re-assessment of the IAB following joint referral from the Directorate General for Health, the Directorate of Social Security and the Directorate General of Health Services on 10 October 2013, in accordance with article R 163-19 of the French Social Security Code.**
List(s) concerned	**Hospital use** (French Public Health Code L.5123 2)
Indication(s) concerned	**"BEROMUN is indicated in adults, used in combination with melphalan for mild hyperthermic isolated limb perfusion for the treatment of soft tissue sarcoma of the limbs:** **- for subsequent removal of the tumour so as to prevent or delay amputation;** **- in the palliative situation, for irresectable soft tissue sarcoma."**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**In view of the available data, the Committee considers that the BEROMUN/melphalan combination provides:** **- a minor IAB (level IV) in the treatment of soft tissue sarcoma of the limbs for subsequent removal of the tumour, so as to prevent or delay amputation,** **- a minor IAB (level IV) in irresectable soft tissue sarcoma.**
Therapeutic use	**BEROMUN combined with melphalan is a first-line treatment for locally advanced limb sarcomas with a risk of amputation or functionally mutilating surgery.**
Transparency Committee recommendations	**The Transparency Committee would like to have additional data, within 2 years, documenting the therapeutic value of tasonermin (BEROMUN) under actual conditions of use. These data concern:** **- the characteristics of the patients treated, in particular age, sex, disease stage,** **- the conditions of use for BEROMUN: reasons for starting treatment, prescribed dosage and follow-on treatments.** **- the impact on morbidity and mortality, in particular on the outcome for patients who received an isolated limb perfusion and the functional outcome for the treated limb as well as quality of life data.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	13 April 1999 (centralised procedure)
Prescribing and dispensing conditions/special status	List I Reserved for hospital use. Medicine requiring special monitoring during treatment.

ATC Classification	2013	
	L:	Antineoplastic and immunomodulating agents
	L03:	Immunostimulants
	L03A:	Cytokines and immunomodulators
	L03AX:	Colony-stimulating factors
	L03AX11:	tasonermin

02 BACKGROUND

As part of the work aimed at updating the list of chargeable medicinal products in addition to hospital services by the French Hospital Financial Advisory Board, and pursuant to article R 163-19 of the French Social Security Code, the Directorate General for Health, the Directorate of Social Security and the Directorate General of Health Services has applied to HAS for a ruling on the IAB of proprietary medicinal products, including the proprietary medicinal product **BEROMUN, powder for solution for infusion**, subject of this opinion. Due to the length of inclusion, starting during a time when the IAB was not part of the assessment as it is today, this criterion had not been assessed by the Committee.
The proprietary medicinal product BEROMUN 2 mg, powder for solution for infusion, was included on the list of medicines approved for use by hospitals and various public services by the decision of 17 October 2001 (Official Gazette of 26 October 2001).
By decree of 4 April 2005, published in the Official Gazette of 10 May 2005, this proprietary medicinal product was included on the list of chargeable medicinal products in addition to hospital services

03 THERAPEUTIC INDICATIONS

"BEROMUN is indicated in adults, used in combination with melphalan for mild hyperthermic isolated limb perfusion for the treatment of soft tissue sarcoma of the limbs:
- for subsequent removal of the tumour so as to prevent or delay amputation;
- in the palliative situation, for irresectable soft tissue sarcoma."

04 DOSAGE

"BEROMUN:
Upper limb: 3 mg total dose by ILP
Lower limb: 4 mg total dose by ILP

Melphalan:
Melphalan dose should be calculated according to the litre-volume method of Wieberdink (Wieberdink J, Benckhuysen C, Braat RP, van Slooten EA, Olthius GAA. Dosimetry in isolation perfusion of the limbs by assessments of perfused tissue volume and grading of toxic tissue reactions. Eur J Cancer Clin Oncol 1982; 18: 905-910.), to a maximum dose of 150 mg.
13 mg/l perfused upper limb volume
10 mg/l perfused lower limb volume

Paediatric population
The safety and efficacy of BEROMUN in children under 18 years have not been established. No data are available. "

05 THERAPEUTIC NEED

Soft tissue sarcomas (STS) are rare disorders. They represent less than 1% of all malignancies in adults. Around 50% of STS are located in the upper or lower limbs. Due to their asymptomatic nature, STS may be large by the time they are diagnosed.[1]
Soft tissue sarcomas may take very different forms and are likely to invade nearby tissues and organs and cause local complications: gastrointestinal obstruction, paralysis, difficulty moving joints, etc.
Patients with soft tissue sarcoma of the limbs have a high risk of local or systemic relapse. Depending on the local situation of the limb, the patient may require extensive and mutilating surgery. Limb amputation has not shown an increase in patient survival.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There are no pharmacological comparators for this proprietary medicinal product.

06.2 Other health technologies

None

◗ Conclusion

There are no clinically relevant comparators for this proprietary medicinal product.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

[1] Jemal A, Siegel R, Ward E, Hao Y, Xu J and Thun MJ: Cancer statistics, 2009. CA Cancer J Clin 59: 225-249, 2009.

Country	Reimbursement	
	Yes/No	Scope (indications) and special condition(s)
Germany	Yes	Indication in MA
Belgium	Yes	same
Denmark	No	Not applicable
Greece	No	Not applicable
Ireland	Yes	Indication in MA
Italy	Yes	same
Netherlands	Yes	same
United Kingdom	Yes	same

08 SUMMARY OF PREVIOUS ASSESSMENTS

◗ Inclusion of BEROMUN on the list of proprietary medicinal products approved for use by hospitals and various public services.

Indication	"BEROMUN is indicated in adults, used in combination with melphalan for mild hyperthermic isolated limb perfusion for the treatment of soft tissue sarcoma of the limbs: - for subsequent removal of the tumour so as to prevent or delay amputation; - in the palliative situation, for irresectable soft tissue sarcoma."
Date of opinion (reason for the request)	5 September 2001
Therapeutic value	Given the conserving surgery rate obtained, BEROMUN in combination with melphalan has a significant role in the treatment of soft tissue sarcoma of the limbs: - for subsequent removal of the tumour so as to prevent or delay amputation - in the palliative situation, for irresectable soft tissue sarcoma.
Therapeutic use	This treatment will be set up in specialised facilities, by teams experienced in the treatment of limb sarcomas and very familiar with the isolated limb perfusion technique. These hospitals must have an intensive care unit and all the necessary equipment to continuously detect passage of the medicine into the systemic circulation.
Target population	Unspecified.

09 ANALYSIS OF AVAILABLE DATA

As part of the reassessment of BEROMUN (tasonermin), the company has provided a literature dossier including:
- a single-centre study (Grabellus, 2011[2]) conducted in 53 patients with soft tissue sarcoma and whose main objective was to study the correlation between the response to isolated limb perfusion (ILP) treatment histopathologically and basic patient characteristics, including microvessel density in the initial tumour. Given its objective, this study is not likely to provide precise information on the efficacy and safety of BEROMUN in this indication, and it will therefore not be considered in detail in this opinion.
- two literature reviews (Taeger, 2008 and Verhoef, 2007), presented below.

09.1 Efficacy

A/ Summary of the data assessed in the TC Opinion of 05/09/2001:

Four non-comparative studies included 188 patients with soft tissue sarcoma of the limbs.
The patients were treated with the BEROMUN + melphalan combination by isolated limb perfusion in two studies and the BEROMUN + melphalan + interferon gamma combination in two other studies.
In the two BEROMUN + melphalan studies (indication in the Marketing Authorisation), the limb salvage rates were 82% and 83%.
In the two BEROMUN + melphalan + interferon gamma studies, the limb salvage rates were 74% and 87%.
A case-control analysis did not evidence a significant difference in terms of overall survival between patients treated with BEROMUN and melphalan in isolated limb perfusion (ILP) and controls.
The most common adverse effects were:

- fever, generally low to moderate, in the majority of patients,
- nausea and vomiting, arrhythmia, asthenia, chills, hepatotoxicity and infections in more than 10% of cases,
- local reactions: skin reactions, oedema, pain in the treated limb, nerve damage, infection of the wound in more than 10% of cases.

B/ New data filed

Two literature reviews
According to the literature data published between 1996 and 2006, reporting the results obtained in cohorts of varying sizes (from 20 to 270 patients), the tumour response rate obtained after treatment with BEROMUN was between 16 and 42% for complete response, 17% to 68% for partial response and 65 to 97% for limb salvage, depending on the publication (see Table 1 from the 2008 Taeger et al publication[3]). Similar results are reported in a prior review by Verhoef, 2007 et al,[4] based on the same studies for the most part.

Table 1: Efficacy results observed with various ILP protocols (Taeger et al. review, 2008)

[2] Grabellus F, Kraft C et Sheu-Grabellus S. Tumor vascularization and histopathologic regression of soft tissue sarcomas Treated with isolated limb perfusion with TNF-α and melphalan. Journal of surgical oncology 2011; 103:371-379.
[3] Taeger G, Grabellus F et Podleska LE. Effectiveness of regional chemotherapy with TNF-α and melphalan in advanced soft tissue sarcoma of the extremities. Int. J. Hyperthermia, May 2008; 24(3): 193-203
[4] Verhoef C, de Wilt J and Grühagen D. Isolated limb perfusion with melphalan and TNF-α in the treatment of extremity sarcoma. Current treatment options in oncology 2007; 8:417-27.

	Type of ILP treatment	Number of patients	CR (%)	PR (%)	Limb salvage (%)
Eggermont et al.,1996[5]	TNF-α+IFN+mel	195	18	64	84
Eggermont et al.,1999[6]	TNF-α+mel	270	28	48	76
Eggermont et al., 1999[7]	TNF-α+mel	196	17	48	71
Gutman et al., 1997[8]	TNF-α+mel (+IFN)	35	37	54	85
Olieman et al., 1999[9]	TNF-α+mel	34	35	59	85
Lev-Chelouche et al., 1999[10]	TNF-α+mel	53	38	54	85
Rossi et al., 1999[11]	TNF-α+dox	20	26	64	85
Lejeune et al., 2000[12]	TNF-α+mel	22	18	64	77
Noorda et al., 2003[13]	TNF-α+mel (+IFN)	49	8	55	58
Lans et al., 2005[14]	TNF-α+mel	30	20	50	65
Grunhagen et al., 2005[15]	TNF-α+mel	64	42	45	82
Rossi et al., 2005	TNF-α+dox	21	55	35	71
Bonvalot et al., 2005	TNF-α+mel*	100	49	17	87
Grunhagen et al., 2006	TNF-α+mel*	217	16	68	97

CR: Complete response; PR: Partial response; ILP: isolated limb perfusion
TNF-α: tasonermin, IFN: interferon gamma, Mel: melphalan, Dox: doxorubicin
** TNF-α dose reduced to 1 mg

[5] Eggermont AM, Schraffordt KH, Klausner JM et al.: Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. Ann Surg 1996;224:756–64.
[6] Eggermont AM, Schraffordt KH, Klausner JM et al. Limb salvage by isolated limb perfusion with tumor necrosis factor alpha and melphalan for locally advanced extremity soft tissue sarcomas: Results of 270 perfusions in 246 patients. Proc Am Soc Clin Oncol USA 1999;11:497
[7] Eggermont AM et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas: the cumulative multicenter European experience. Ann Surg 1996;224: 756-64
[8] Gutman M, Inbar M, Lev-Shlush D, Abu-Abid S, Mozes M, Chaitchik S, Meller I, Klausner JM. High dose tumor necrosis factor-alpha and melphalan administered via isolated limb perfusion for advanced limb soft tissue sarcoma results in a 490% response rate and limb preservation. Cancer 1997;79:1129–37.
[9] Olieman AF, Pras E, van Ginkel RJ, Molenaar WM, Schraffordt KH, Hoekstra HJ. Feasibility and efficacy of external beam radiotherapy after hyperthermic isolated limb perfusion with TNF-alpha and melphalan for limb-saving treatment in locally advanced extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 1998;40:807–14.
[10] Lev-Chelouche D, Abu-Abeid S, Kollander Y, Meller I, Isakov J, Merimsky O, Klausner JM, Gutman M. Multifocal soft tissue sarcoma:Limb salvage following hyperthermic isolated limb perfusion with high-dose tumor necrosis factor and melphalan. J Surg Oncol 1999;70:185–9.
[11] Rossi CR, Foletto M, Di Filippo F, Vaglini M, Anza' M, Azzarelli A, Pilati P, Mocellin S, Lise M. Soft tissue limb sarcomas: Italian clinical trials with hyperthermic antiblastic perfusion. Cancer 1999;86:1742–9.
[12] Lejeune FJ, Pujol N, Lienard D et al. Limb salvage by neoadjuvant isolated perfusion with TNFalpha and melphalan for non-resectable soft tissue sarcoma of the extremities. Eur J Surg Oncol 2000; 26:669–78.
[13] Noorda EM, Vrouenraets BC, Nieweg OE, Coeforden van C, van Slooten GW, Kroon BB. Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. Cancer 2003;98:1483-90.
[14] Lans TE, Grunhagen DJ, de Wilt JH, van Geel AN, Eggermont AM. Isolated limb perfusions with tumor necrosis factor and melphalan for locally recurrent soft tissue sarcoma in previously irradiated limbs. Ann Surg Oncol 2005; 12:406–11.
[15] Grunhagen DJ, de Wilt JH, van Geel AN, Graveland WJ, Verhoef C, Eggermont AM. TNF dose reduction in isolated limb perfusion. Eur J Surg Oncol 2005;31: 1011-19.

09.2 Safety/Adverse effects

The literature data update confirmed the known safety profile of tasonermin.
The French pharmacovigilance data are consistent with the international data reported during the same period covered by the first three PSURs (covering the period from 14 October 2003 to 14 November 2011). No new safety signals were evidenced.
The three system organ classes having the most adverse events noted in the latest PSUR were "vascular disorders" (14.7%), "general disorders and administration site conditions" (14.1%) and "neoplasms benign and malignant" (8%).
In November 2012, section 4.8 of the SPC was updated by adding peripheral arterial occlusive diseases with rare occurrence.

09.3 Usage/prescription data

Given the orphan nature of the disease and the low number of sales, the conditions for use for BEROMUN cannot be documented from prescription panels.

For information purposes, the GERS [Partnership for the collection and Preparation of Statistics] hospital sales data (in common units of dispensation) covering the period from January 2013 to December 2013 are presented in the table below:

Table 2: GERS hospital sales data

Wording	Common units of dispensation First quarter	Common units of dispensation Second quarter	Common units of dispensation Third quarter	Common units of dispensation Fourth quarter
BEROMUN	16	12	0	8

09.4 Summary & discussion

Four non-comparative studies included 188 patients with soft tissue sarcoma of the limbs.
The patients were treated with the BEROMUN + melphalan combination by isolated limb perfusion in two studies and the BEROMUN + melphalan + gamma interferon combination in two other studies. In the two studies where BEROMUN was combined with melphalan according to the regimen in the Marketing Authorisation, the limb salvage rates were 82% and 83%.
A case-control analysis did not evidence a significant difference in terms of overall survival between patients treated with BEROMUN and melphalan in isolated limb perfusion (ILP) and controls.
The literature data published between 1996 and 2006 confirm these results; the tumour response rate obtained after treatment with BEROMUN varied from 16 to 42% for complete response, 17% to 68% for partial response, and 65 to 97% for limb salvage depending on the publication.

The Committee emphasises the absence of data, especially on the outcome of patients treated with BEROMUN as an adjuvant (the functionality of the perfused limb, immediate or delayed effects, etc.) and quality of life for metastatic stages.

The most common adverse effects in the pivotal studies were:
- fever, generally low to moderate, in the majority of patients,
- nausea and vomiting, arrhythmia, asthenia, chills, hepatotoxicity and infections in more than 10% of cases,
- local reactions: skin reactions, oedema, pain in the treated limb, nerve damage, infection of the wound in more than 10% of cases.

09.5 Planned studies

No studies are currently in progress or forthcoming.

010 THERAPEUTIC USE

Several studies have shown that amputating a limb affected by soft tissue sarcoma does not change overall survival. Chemotherapy administered by isolated limb perfusion (ILP) is indicated for advanced limb sarcomas with a risk of amputation or functionally mutilating surgery. This ILP is administered either as a neoadjuvant, and in the event of very good response, the patient is then operated on, or without subsequent excision surgery, for palliative purposes, if the goal is to avoid an amputation with a metastatic patient.
Systemic chemotherapy (reserved for high grades in patients in good general condition) does not lead to equally high objective response rates on the primary tumour. Nevertheless, it may be done sequentially in patients with a risk of metastasis.
Radiation therapy is not standard preoperatively; it is done when the topography of the tumour does not permit perfusion of the limb and to reduce tumour volume. Conventionally, it is proposed after tumour excision, depending on the histopathology (surgical margins, topography, etc.).

The loco-regional administration of tasonermin (BEROMUN) in combination with melphalan has proven very effective on the local outcome of irresectable soft tissue sarcomas of the limbs. However, this treatment remains specifically loco-regional and has no influence on global patient survival. A case-control analysis did not evidence a difference in terms of survival (p=0.5) between patients treated with tasonermin combined with melphalan by ILP (isolated limb perfusion) and controls.[16]

[16] BEROMUN SPC

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

- Soft tissue sarcoma is a serious and life-threatening disorder.
- This is specific curative or palliative treatment for soft tissue cancer.
- The efficacy/adverse effects ratio is high.
- There is no pharmacological treatment alternative.
- It is a first-line therapy.
    - Public health benefit:

    Soft-tissue sarcomas are serious pathologies that may be life-threatening. The subpopulation concerned by the indication for BEROMUN is a low public health burden because of its rarity. Improving the management of these diseases is a public health need that is an established priority (GTNDO,[17] Rare Diseases Plan, lack of alternative treatments).
    In view of the limited clinical data and the absence of formal comparisons versus historical cohorts at a minimum, the expected impact of the proprietary medicinal product BEROMUN in terms of morbidity/mortality and quality of life in these patients is difficult to quantify. It is impossible to know whether or not this proprietary medicinal product meets an identified public health need.
    In the current state of knowledge, BEROMUN is not expected to have an impact on public health.

Taking account of these points, the Committee considers that the actual benefit of BEROMUN is substantial in the indication "treatment of soft tissue sarcoma of the limbs:
- for subsequent removal of the tumour so as to prevent or delay amputation;
- in the palliative situation, for irresectable soft tissue sarcoma. "

011.2 Improvement in actual benefit (IAB)

In view of the available data, the Committee considers that the BEROMUN/melphalan combination provides:

- **a minor IAB (level IV) in the treatment of soft tissue sarcoma of the limbs for subsequent removal of the tumour, so as to prevent or delay the amputation,**
- **a minor IAB (level IV) in irresectable soft tissue sarcoma.**

[17] Groupe Technique National de Définition des Objectifs [National Technical Group for the Definition of Public Health Objectives] (Directorate General for Health 2003)

011.3 Target population

The target population for BEROMUN is defined by adult patients with soft tissue sarcoma of the limbs requiring isolated limb perfusion with surgical resection of the tumour, in order to prevent or delay amputation or for palliative purposes, for irresectable sarcomas.
Sarcomas are rare tumours with an incidence of approximately 6 new cases per 100,000 individuals per year,[18] which corresponds to approximately 4,000 estimated new cases per year in France.
Approximately 50% of STS are located in the upper or lower limbs, which represents approximately 2000 new cases a year.
It is difficult to estimate the exact number of patients with soft tissue sarcoma of the limbs requiring isolated limb perfusion before surgical resection of the tumour, in order to prevent or delay amputation or for palliative purposes, for irresectable sarcomas.

However, experts believe that this proprietary medicinal product would target about ten patients a year.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee would like to have additional data, within 2 years, documenting the therapeutic value of tasonermin (BEROMUN) under actual conditions of use. These data concern:
- the characteristics of the patients treated, in particular age, sex, disease stage,
- the conditions of use for BEROMUN: reasons for starting treatment, prescribed dosage and follow-on treatment.
- the impact on morbidity and mortality, in particular on the outcome for patients who received an isolated limb perfusion and the functional outcome for the treated limb as well as quality of life data.

[18] Verhaeghe JL, Rios M, Leroux A, Sirveaux F, Henrot P, Blum A, Marchal F. Traitement des sarcomes des tissus mous de l'adulte : quelle stratégie pour optimiser le traitement. e-mémoires de l'Académie Nationale de Chirurgie [Treatment of soft tissue sarcomas in adults: the strategies for optimising treatment. e-briefs of the National Academy of Surgery] 2011; 10: 048-053.