IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. A11-27

Collagenase clostridium histolyticum – Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Mikrobielle Collagenase aus Clostridium histolyticum – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 30.01.2012). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Collagenase clostridium histolyticum – Benefit assessment according to § 35a Social Code Book V

Contracting agency:

Federal Joint Committee

Commission awarded on:

02.11.2011

Internal Commission No.:

A11-27

Address of publisher:

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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Keywords: collagenases, Dupuytren's contracture, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PF	partial fasciectomy
PNF	percutaneous needle fasciotomy
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 16.11.2011, in accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the active substance collagenase *clostridium histolyticum* (abbreviated to "collagenase" below) in the treatment of Dupuytren's contracture. The assessment was based on a dossier compiled by the pharmaceutical company. The dossier was sent to IQWiG on 16.11.2011.

Research question

The benefit assessment of the active substance collagenase was carried out for the approved therapeutic indication "Dupuytren's contracture in adult patients with a palpable cord" [1].

The G-BA specified the following appropriate comparator therapies (ACTs), depending on the severity of the disease (Tubiana's classification):

Therapeutic indication of collagenase subdivided according to Tubiana's stages of Dupuytren's contracture	**Appropriate comparator therapy**
1. Stage N (palpable nodules or cords, no contracture)	No treatment
2. Stages N/I, I and II (contracture ≤ 90°)	Percutaneous needle fasciotomy (PNF)
3. Stages III and IV (contracture > 90°)	Partial fasciectomy (PF)
4. Stages III and IV, with contraindication for PF	Percutaneous needle fasciotomy (PNF)

The pharmaceutical company did not follow the G-BA specifications with regard to the comparator therapies, but instead chose PF as the sole ACT for all treatment-requiring stages of the disease. The Institute considers this deviation from the G-BA requirements as inadequately justified. The benefit assessment of collagenase was therefore carried out using the ACTs specified by the G-BA, thus producing a total of 4 research questions (divided according to severity).

Results

The pharmaceutical company carried out no evaluation regarding the first research question ("Collagenase vs. no treatment in patients with Tubiana's Stage N"), neither did the company's list of studies contain studies on this comparison.

Likewise, the company failed to undertake any evaluation of the second and fourth research questions ("Collagenase vs. PNF in patients with Tubiana's Stage N/I to II" and "Patients

with Tubiana's Stage III or IV with contraindication for PF"). Again, the list of studies provided by the company contained no studies on these comparisons.

In the case of the third research question ("Patients with Tubiana's Stage III or IV without contraindication for PF"), the comparator therapy used by the company corresponded with the ACT specified by the G-BA (PF). The company did not submit any direct comparative studies concerning this research question, but carried out an indirect comparison between collagenase and PF over all degrees of severity of the disease and addressed the patient group of interest (Tubiana's Stage III and IV) by means of subgroup analyses. Although the company identified 3 randomized controlled trials (RCTs) on PF, the absence of a common intermediate comparator meant that no adjusted indirect comparison between collagenase and PF could be conducted. As a substitute, the company carried out a non-adjusted indirect comparison. However, only one of the identified RCTs with the PF included conclusions about the patient group of interest (Tubiana's Stage III and IV). These merely concerned results for a single outcome (postoperative residual contracture), which was not recorded in the studies with collagenase and from which no comparative conclusions between collagenase and the PF regarding benefit (e.g. on functional capacity) or harm can be inferred. Thus there is neither an evaluable non-adjusted indirect comparison nor relevant RCT for such a comparison. Moreover, the company submitted additional results of non-randomized studies on PF, in order to obtain conclusions on rates of recurrence and complications. Apart from the fact that the company's related search is unsuitable, its evaluation provides no relevant data on the patient group of interest (Tubiana's Stage III and IV).

In summary, no relevant study is available for any of the 4 research questions and hence no suitable indirect comparison is available either. There is therefore no proof of an added benefit for any of the 4 patient groups.

Probability and extent of the added benefit, patient groups with therapeutically important added benefits

The available data provides no proof of an added benefit of collagenase in comparison with the various ACTs specified by the G-BA for any group of patients. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

The benefit assessment of collagenase was carried out for the approved therapeutic indication "Dupuytren's contracture in adult patients with a palpable cord" [1].

In the dossier, the pharmaceutical company designated partial fasciectomy (PF) as the ACT for the whole therapeutic indication of Dupuytren's contracture. By doing so, it deviated from the G-BA's requirement, which subdivided the therapeutic indication according to Tubiana's classification [2,3] and specified the particular ACT suitable for each stage (Table 1).

Table 1: Summary of the appropriate comparator therapies of the G-BA and the pharmaceutical company

Therapeutic indication of collagenase subdivided according to Tubiana's stages of the Dupuytren's contracture	**Appropriate comparator therapy of the G-BA**	**Appropriate comparator therapy used by the pharmaceutical company**
Stage N (palpable nodules or cords, no contracture)	No therapy	Partial fasciectomy
Stages N/I, I and II (contracture ≤ 90°)	Percutaneous needle fasciotomy	Partial fasciectomy
Stages III and IV (contracture > 90°)	Partial fasciectomy	Partial fasciectomy
Stages III and IV (contracture > 90°), with contraindication for PF	Percutaneous needle fasciotomy	Partial fasciectomy
G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee), PF: partial fasciectomy		

In the Institute's view – which is presented in detail in Section 2.7.1 of the full assessment – the pharmaceutical company does not provide adequate justification for this deviation. Therefore IQWiG used the ACTs specified by the G-BA for the benefit assessment of collagenase, which gives rise to a total of 4 research questions (subdivided according to severity).

The assessment was carried out in relation to patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval, study pool and studies included in the assessment

The study pool of the assessment was compiled from the following information:

- Studies of collagenase completed by the pharmaceutical company up to 06.10.2011 (company list of studies).
- Results of a bibliographical literature search and a search in trial registries for collagenase and for partial fasciectomy (last search 06./07.09.2011 in bibliographical databases and 11.01. and 05./06.09.2011 in trial registries, company searches).
- An independent search for studies of collagenase by the Institute in bibliographical databases and trial registries and for partial fasciectomy in trial registries to check the company's search results up to 21./22.11.2011. The check produced no additional relevant study.

The company also conducted searches in bibliographical databases to identify relevant non-randomised studies with the query “Identification of studies on the recurrence rate and safety of treatment”. However, this search is inadequate and therefore cannot be used (see Comments in 2.7.2.3 of the full dossier assessment).

The named steps of information retrieval identified no study of relevance to any of the 4 research questions. The reasons for this are as follows:

The pharmaceutical company undertook no evaluation relating to the first research question (“Collagenase vs. no treatment in patients with Tubiana’s stage N”). For this research question the company did not comply with the ACT specified by the G-BA. The placebo-controlled studies listed by the company cannot be used for assessment, because they included no patients in Stage N.

As regards the second and fourth research questions (“Collagenase vs. PNF in patients with Tubiana’s Stage N/I to II” and “Patients with Tubiana’s Stage III or IV, in whom a PF was contraindicated”) the company also undertook no evaluation, neither did the list of studies compiled by the company contain studies on this comparison.

In the case of the third research question (“Patients with Tubiana’s Stage III or IV without contraindication for PF”), the comparator therapy used by the company corresponded with the ACT specified by the G-BA (PF). The company did not submit any direct comparative studies concerning this research question, but carried out an indirect comparison between collagenase and PF over all degrees of severity of the disease, and addressed the patient group of interest (Tubiana’s Stage III and IV) by means of subgroup analyses. Although the company identified 3 RCTs on PF, the absence of a common intermediate comparator meant that no adjusted indirect comparison between collagenase and PF could be conducted. As a substitute, the company carried out a non-adjusted indirect comparison. However, only one of the identified RCTs with the PF included conclusions about the patient group of interest (Tubiana’s Stage III and IV). These merely concerned results for a single outcome (postoperative residual contracture), which was not recorded in the studies with collagenase and from which no comparative conclusions between collagenase and the PF regarding benefit (e.g. on functional capacity) or harm can be inferred. Thus there is neither a suitable non-adjusted indirect comparison nor relevant RCT for such a comparison. Moreover, the company submitted additional results of non-randomized studies on PF, in order to obtain conclusions on rates of recurrence and complications. Apart from the fact that the company’s related search is unsuitable, its evaluation provides no relevant data on the patient group of interest (Tubiana’s Stage III and IV). Overall, no study of relevance to the fourth research question is available either.

Further information about the inclusion criteria for studies in the present benefit assessment and the methods and results of information retrieval and the study pool derived from it, can be found in Module 4, Sections 4.2.2, 4.2.3, 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.1, 2.7.2.3 and 2.7.2.3.4 of the full dossier assessment.

2.4 Results concerning added benefit

There are no relevant studies for any of the 4 research questions. No conclusions can be drawn regarding the patient group of interest for this comparison (Tubiana's Stage III and IV), neither from the non-adjusted indirect comparison carried out by the company on the basis of RCTs, nor from the other studies on the comparison of collagenase and PF that it submitted.

The RCT-based, non-adjusted indirect comparison conducted by the pharmaceutical company, as well as the supplementary analyses provided by the company for the comparison of collagenase and PF do not allow to draw any conclusions regarding the patient group of interest for this comparison (Tubiana's Stage III and IV).

Overall, there is therefore no proof of an added benefit of collagenase compared with the respective ACT for any degree of severity.

Further information on the choice of outcome and on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier.

2.5 Extent and probability of the added benefit

The current data provide no proof of an added benefit of collagenase in comparison with the respective ACT specified by the G-BA for any group of patients (see Table 2). Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This conclusion deviates markedly from that of the pharmaceutical company, which, for all patient groups, claims a major added benefit of collagenase compared with its chosen comparator therapy.

Table 2: Collagenase: Extent and probability of the added benefit

Therapeutic indication of collagenase subdivided according to Tubiana's stages of the Dupuytren's contracture	**Appropriate comparator therapy**	**Extent and probability of the added benefit**
Stage N (palpable nodules or cords, no contracture)	No therapy	Added benefit not proven
Stages N/I, I and II (contracture ≤ 90°)	Percutaneous needle fasciotomy	Added benefit not proven
Stages III and IV (contracture > 90°)	Partial fasciectomy	Added benefit not proven
Stages III and IV (contracture > 90°), with contraindication for PF	Percutaneous needle fasciotomy	Added benefit not proven
PF: partial fasciectomy		

The decision regarding added benefit is made by the G-BA.

2.6 List of included studies

Not applicable, as the pharmaceutical company did not submit any studies from which an added benefit of collagenase versus the ACTs specified by the G-BA could be determined.

References for English extract (please see full dossier assessment for full reference list)

1) Product information: 28/02/201, Xiapex, EMEA/H/C/002048. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002048/human_med_001423.jsp&mid=WC0b01ac058001d125&murl=menus/medicines/medicines.jsp&jsenabled=true (accessed on 30.03.2012)

2) Tubiana R. Evaluation of deformities in Dupuytren's disease. Ann Chir Main 1986; 5(1): 5-11.

3) Tubiana R. Surgical Treatment. In: Tubiana R (Ed). The Hand. Philadelphia: Saunders; 1999. S. 451-483. (Band IV).

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