



FINAL CDEC RECOMMENDATION

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

(Xiaflex — Auxilium Pharmaceuticals Inc.)

Indication: Dupuytren's Contracture with a Palpable Cord

Recommendation: The Canadian Drug Expert Committee (CDEC) recommends that collagenase clostridium histolyticum (CCH) be listed if all of the following clinical criteria and condition(s) are met:

Clinical Criteria:

1. CCH should be administered by a health care professional with experience in performing hand surgery and treating Dupuytren's contracture.
2. CCH treatment for Dupuytren's contracture is limited to three injections per cord.

Condition: Reduced price

The total cost of CCH should not exceed the cost of alternative treatments for Dupuytren's contracture.

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) demonstrated that CCH was efficacious for the treatment of Dupuytren's contracture with an acceptable safety profile, provided the treatment is administered by a health care professional with experience in performing hand surgery and treating Dupuytren's contracture.
2. There is significant uncertainty in the cost-minimization analysis submitted by the manufacturer comparing CCH with open partial fasciectomy (OPF). A reduced price would increase the probability of CCH being cost-saving compared with OPF.

Of Note:

The total cost of treating Dupuytren's contracture with CCH is highly dependent on the number of injections needed per cord, the number and type of joints being treated, and the severity of the condition. Increasing the total number of injections per patient can result in CCH treatment being more costly than alternative treatments.

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Background:

CCH has a Health Canada indication for the treatment of adult patients with Dupuytren's contracture with a palpable cord. It is available as a lyophilized powder for injection of 0.9 mg/vial. CCH contains collagenase AUX-I and collagenase AUX-II, enzymes that break down collagen. The Health Canada-recommended dose is 0.58 mg per injection into a palpable cord with contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint. Injections may be administered up to three times per cord at approximately four-week intervals if contracture persists.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of CCH, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients. The manufacturer submitted a confidential price for CCH.

Patient Input Information

One patient group responded to the CDR Call for Patient Input. In summary, they stated that:

- CCH administration is a minimally invasive procedure and has been associated with a quick recovery;
- CCH may be a more suitable therapy than percutaneous needle fasciotomy for certain patients; and,
- several visits to the doctor are required for CCH and only one joint of one finger is treated at a time. By comparison, percutaneous needle fasciotomy and surgery can treat several fingers/joints in one treatment session.

Clinical Trials

The systematic review included seven manufacturer-sponsored, double-blind, placebo-controlled RCTs. Two trials (CORD-I and CORD-II) used a treatment regimen for the CCH groups that was consistent with recommendations in the Health Canada-approved product monograph; therefore, these trials were considered the pivotal trials in the CDR review. The other five trials included three phase III RCTs (DUPY-303, AUX-CC 851/852, and AUX-CC 853) and two phase II RCTs (DUPY-101 and DUPY-202). None of the included trials were designed to compare CCH with surgery or percutaneous needle fasciotomy.

CORD-I (N = 308) and CORD-II (N = 66) were identically designed phase III, placebo-controlled, multicentre RCTs that included a three-month randomized, controlled period followed by a nine-month open-label extension period. Patients included were adults with Dupuytren's contracture (at least a 20 degree contracture) with a palpable cord. Randomization was stratified by joint type (MP/PIP) and the severity of contracture at baseline.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- Clinical success — defined as a reduction in contracture to five degrees or less as measured by finger goniometry 30 days after the last injection.
- Clinical improvement — defined as a reduction in contracture of at least 50%.

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- Range of motion — defined as the difference between the full flexion angle and full extension angle expressed in degrees.
- Patient Global Assessment — a patient reported assessment that was administered in the three parts: 1) patients completed a four-point categorical scale to assess self-reported baseline severity; 2) patients rated improvement from baseline on a scale of 0% to 100%, 30 days after the last injection; and 3) patients reported satisfaction with treatment on a five-point scale, 30 days after the last injection, as follows: “very satisfied,” “quite satisfied,” “neither satisfied nor dissatisfied,” “quite dissatisfied,” or “very dissatisfied.”
- Adverse events, serious adverse events, and withdrawals due to adverse events.

The primary outcome in CORD-I and CORD-II was the proportion of patients who achieved clinical success (i.e., a reduction in contracture of their primary joint to five degrees or less at the day 30 evaluation after the last injection of study drug). Quality of life was not evaluated in either CORD-I or CORD-II.

Results

Efficacy

- A significantly larger proportion of CCH-treated patients achieved clinical success compared with placebo-treated patients in both CORD-I (62.7% versus 6.7%, $P < 0.001$) and CORD-II (44.4% versus 4.8%; $P < 0.001$). Similarly, a significantly larger proportion of CCH-treated patients achieved clinical improvement compared with placebo in both CORD-I (84.7% versus 11.7%; $P < 0.001$) and CORD-II (77.8% versus 14.3; $P < 0.001$).
- In the Patient Global Assessment, a greater proportion of CCH-treated patients reported improvement at 30 days after the last injection in both CORD-I and CORD-II compared with placebo-treated patients. Also, a larger proportion of CCH-treated patients reported overall satisfaction with treatment (i.e., “very” or “quite” satisfied) compared with placebo (82% versus 32%, $P < 0.001$ in CORD-I and 87% versus 30%, $P < 0.001$ in CORD-II).
- The difference in percent reduction of contracture from baseline between CCH and placebo was 70% ($P < 0.001$) in CORD-I and 67% ($P < 0.001$) in CORD-II.
- CCH-treated patients showed greater improvement from baseline in range of motion compared with placebo-treated patients in both CORD-I (mean difference 33 degrees, $P < 0.001$) and CORD-II (mean difference 28 degrees, $P < 0.001$).

Harms (Safety and Tolerability)

- Of the patients treat with CCH, 97% to 100% reported at least one adverse event compared with 47% to 57 % of patients treated with placebo. Adverse events were most commonly associated with injection site conditions and most were mild or moderate in intensity and resolved without intervention.
- Serious adverse events were reported for seven CCH-treated patients (3%) and one placebo-treated patient (1%) in CORD-I and one CCH-treated patient (2%) in CORD-II.
- Withdrawals due to adverse events were reported for three CCH-treated patients and no placebo-treated patients in CORD-I. There were no withdrawals due to adverse events reported in CORD-II.

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Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing the cost of CCH injections with OPF. The European Medicines Agency assessments of CCH, and two surgical reviews of OPF and percutaneous needle fasciectomy, were used in a naive indirect comparison to support the assumption of similar clinical efficacy and safety between CCH and OPF. Treatment costs were considered during a five-year time frame. For patients undergoing CCH treatment, a maximum of three injections per cord were considered for a maximum of three cords, capping the cost of treatment at *[confidential price removed at manufacturer's request]*. The manufacturer estimated a cost saving of \$639 per patient when comparing CCH with OPF.

CDR noted the following limitations with the manufacturer's analysis:

- The manufacturer identified percutaneous needle fasciectomy as a comparator, but excluded it from their analysis. Given that the technique is gaining popularity for the treatment of MP joints, it represents a reasonable comparator.
- The use of CCH in actual practice is unknown. Given there are no restrictions in the product monograph on the number of cords that may be treated, the cost of CCH could vary greatly by patient.

At the submitted confidential price, the cost of CCH (*[confidential price removed at manufacturer's request]*) is highly dependent on its use (i.e., the number of cords treated).

Other Discussion Points:

The Committee noted the following:

- There is insufficient evidence to determine the place in therapy for CCH relative to surgery or percutaneous needle fasciectomy.
- CORD-I and CORD-II did not report subgroup data for patients who had undergone prior surgical treatment for Dupuytren's contracture or for patients who are ineligible for surgical treatment of Dupuytren's contracture.
- Long-term recurrence of Dupuytren's contracture could not be estimated from the controlled phases of CORD-I and CORD-II.

Research Gaps:

The Committee noted that there is an absence of evidence regarding the following:

- There is no direct comparison between CCH and surgery or percutaneous needle fasciotomy for the treatment of Dupuytren's contracture.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:

January 16, 2013 Meeting
None

March 20, 2013 Meeting
One CDEC member could not attend the meeting.

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a Record of Advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

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