

# Clinical Research Overview

## BCM-95® / CURCUGREEN™

### TURMERIC RHIZOME / CURCUMIN EXTRACT PREPARATION

*Curcuma longa* L. syn. *C. domestica* Valetton  
[Fam. Zingiberaceae]

#### OVERVIEW

This Clinical Research Overview is based on the full monograph covering the published scientific and clinical research on BCM-95® (also known as Curcugreen™), a proprietary preparation made from turmeric rhizomes (underground stems, sometimes referred to as roots) formulated by Arjuna Natural Extracts Ltd. of Alwaye, Kerala, India. BCM-95 contains an extract characterized as a 95% curcuminoid complex (composed of curcumin, demethoxycurcumin, and bisdemethoxycurcumin in their natural ratios), to which turmeric essential oil is added. The final BCM-95/Curcugreen blend contains no less than 86% total curcuminoids and 65% curcumin, and the essential oil in the blend contains approximately 45% ar-turmerone.

In 2017, dietary supplements with turmeric as the primary ingredient were the top-selling supplements natural retail outlets (e.g., natural food stores) in the United States. Turmeric-containing dietary supplements also ranked 6th in sales in mainstream retail stores (e.g., drugstores, grocery stores) in 2017, with a 46.7% increase in sales in this channel from the previous year.

#### USES

Clinical research conducted with various curcumin preparations indicate therapeutic benefits for a multitude of inflammatory-based disorders (e.g., arthritis), wound healing, diabetes, Alzheimer's disease, cardiovascular disease, and cancer. This monograph covers only those clinical studies conducted on BCM-95, an ingredient which was developed with the goal of improving the bioavailability of curcumin. BCM-95 has been clinically evaluated for the following conditions: major depressive disorder, cognitive health, Alzheimer's disease, osteoarthritis, rheumatoid arthritis, oral submucous fibrosis, oral leukoplakia, and to mitigate adverse effects from radiation therapy in patients with prostate cancer.

#### PHARMACOLOGICAL ACTIONS

Pharmacological studies employing in vitro and in vivo models have found that BCM-95 has antioxidant, anti-inflammatory, antibacterial, and cytotoxic/antitumor actions. Animal studies investigating BCM-95's potential antidepressant, antiepileptic, and hepatoprotective properties have also been conducted.

#### DOSAGE & DURATION OF ADMINISTRATION

The following doses were used in the clinical trials reported in the table in the full monograph. [Note: Most of the doses were used in a single study.]

*Major depressive disorder:* 500 mg/day and 1,000 mg/day

*Cognitive health:* 1,500 mg/day

*Alzheimer's disease:* 1,000 mg/day and 4,000 mg/day

*Osteoarthritis:* 1,000 mg/day

*Rheumatoid arthritis:* 1,000 mg/day

*Oral submucous fibrosis:* 1,000 mg/day

*Oral leukoplakia:* 3,600 mg/day

*Mitigation of adverse effects in patients undergoing radiation treatment for prostate cancer:* 3,000 mg/day

BCM-95 has been administered daily in clinical studies for periods of six weeks to one year. The most common duration of use was 12 weeks; however, long-term use may be acceptable. Experience with the use of turmeric and/or curcumin as a traditional food or medicine does not indicate any limitation on the duration of use.

#### MANUFACTURER DOSE RECOMMENDATIONS

The manufacturer's website does not list a specific recommended dose of BCM-95. The most common dosage used in human clinical trials was 500 mg twice daily.

#### CONTRAINDICATIONS & PRECAUTIONS

There are no known contraindications for BCM-95.

The American Herbal Products Association's *Botanical Safety Handbook*, 2nd ed., lists turmeric as Class 1 (herbs that can be safely consumed when used appropriately) and Interaction Class A (herbs for which no clinically relevant interactions are expected). Mills and Bone, in their book *The Essential Guide to Herbal Safety*, list turmeric as Pregnancy Category A (no proven increase in frequency or malformation or other harmful effects on the fetus despite consumption by a large number of women) and Lactation Category C (compatible with breastfeeding). They contraindicate turmeric preparations in cases of obstruction of the biliary tract and advise to consult a health care professional if someone has gallstones. Adverse reactions associated with oral intake are listed as frequent bowel movements and mild gastric discomfort. The authors advise against combining amounts greater than 15 g turmeric powder per day with antiplatelet or anticoagulant medications.

#### ADVERSE EFFECTS

There is strong evidence of the overall safety of BCM-95. The US Food and Drug Administration accepted the notification of the self-determination of BCM-95 as Generally Recognized as Safe (GRAS) in a no objection letter from the U.S. FDA, dated July 11, 2017.

Clinical studies that used a dose of 500 mg twice daily for eight weeks to three months reported that BCM-95 was administered safely. In one study, BCM-95 was administered in a dose of 4 g daily for six months without significant adverse effects (AEs). The AEs in this study were considered mild; the most common were gastrointestinal complaints, followed by respiratory tract infections and falls or dizziness.

Phase I human clinical studies indicate that curcumin is not toxic even at a very high dose of 12 g per day. The reported adverse events were mild including diarrhea, headache, rash, and yellow stools. (The maximum tolerated dose could not be determined in this study because amounts more than 12 g could not be consumed comfortably.)

## DRUG INTERACTIONS

Some preclinical data indicate that co-administration of curcumin with nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulant drugs might result in an increased risk of bleeding. In a human clinical study, BCM-95 was co-administered with the NSAID diclofenac sodium without producing any significant adverse effects. However, any potential effects of the combination therapy on the risk of bleeding was not part of the evaluation. Curcumin may also interfere with drugs metabolized by the CYP enzyme system, according to data from in vitro experiments using enzymes and human cell lines. Only two clinical studies have explored the effects of standard curcumin on enzymes involved in drug metabolism, and further studies are needed to determine the clinical significance of these reports.

## CLINICAL REVIEW

As of November 2017, there were a total of 10 published human clinical trials on BCM-95 as a monopreparation or as an ingredient in a combination formula. They evaluated the following: major depressive disorder (three studies), cognitive health (one study), Alzheimer's disease (one study), osteoarthritis (one study), rheumatoid arthritis (one study), oral submucous fibrosis (one study), oral leukoplakia (one study), and radiation therapy for prostate cancer (one study).

### Depression

Three randomized, placebo-controlled clinical studies conducted on the effect of BCM-95 on major depression reported favorable results. A single-blind study (N = 45) indicated that BCM-95 (1 g/day) was equal to the pharmaceutical antidepressant fluoxetine (20 mg/day) as measured using HAM-D17 scores. A double-blind study (N = 52) found that BCM-95 (1 g/day) was superior to placebo for subjects with major depression (particularly for a subgroup with atypical depression) as measured using IDS-SR<sub>30</sub> and STAI scores beginning after four weeks of supplementation. Another double-blind study (N = 111) explored treatment with half the usual dose of BCM-95 (0.5 g/day) and found it to be just as effective against depression (measured using IDS-SR30 and STAI scores) as the full dose.

### Cognition

Two placebo-controlled studies that examined the potential benefits of BCM-95 on cognition did not show benefits. A 12-month, randomized, double-blind, placebo-controlled study

(N = 96), in which elderly, cognitively healthy subjects received BCM-95 (1.5 g/day) or placebo, failed to demonstrate an effect on cognition, mood, or general quality of life. An obstacle was that the placebo group did not experience a decline in cognitive function as was expected. A second study (N = 27) conducted with patients with probable or possible Alzheimer's disease was complicated by the fact that both treatment and control groups received a standardized ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract, which, depending on the specific extract, has been reported to have a positive effect on cognition. The six-month study failed to show benefit from additional daily treatment with BCM-95 or another curcumin product at daily doses of 1 or 4 g.

## Joint Health

Two controlled studies compared the effects of treatment with BCM-95 to standard treatment (no placebo control group) in subjects with osteoarthritis or rheumatoid arthritis. A 12-week randomized, two-arm, open-label study (N = 28) in which subjects with osteoarthritis of the knee were administered either 1 g/day Rhulief<sup>®</sup> (a combination product containing BCM-95 and an extract of boswellia [*Boswellia serrata*, Burseraceae]) or 200 mg/day celecoxib found similar benefits resulting from both treatments. A separate 8-week, randomized, two-arm, open-label study (N = 45) of patients with rheumatoid arthritis who received BCM-95 (1 g/day), diclofenac sodium (100 mg/day), or both therapies found that all three treatments were equally effective in reducing disease scores, with a significantly better safety profile for BCM-95 compared to diclofenac sodium.

## Cancer Chemopreventive Effects

Oral submucous fibrosis (OSMF) is a chronic precancerous condition associated with the chewing of betel quid, which is a combination of areca palm (*Areca catechu*, Arecaceae) nuts wrapped in betel (*Piper betle*, Piperaceae) leaves with slaked lime, often in addition to tobacco (*Nicotiana tabacum*, Solanaceae) or spices. An open-label study (N = 32) explored the potential benefits of BCM-95 (1 g/day) or turmeric oil (24 drops/day) compared to a control of spirulina (*Arthrospira maxima*, Oscillatoriaceae) tablets. After three months, there was a measured improvement in clinical symptoms and in histopathology following treatment with BCM-95 and with turmeric oil compared to the control.

Oral leukoplakia is a potentially malignant white lesion of the oral cavity mucosa. A 6-month, randomized, double-blind placebo-controlled trial (N = 223) compared BCM-95 (3.6 g/day) to placebo (cellulose) in subjects with lesions more than 15 mm<sup>2</sup> in size. The BCM-95 group experienced a significant reduction in the size of lesion compared to the placebo group. There was no change in histopathology for either group.

## Radiation therapy

A 20-week, randomized, double-blind placebo-controlled study (N = 40) examined the effects of BCM-95 (3 g/day) on patients with prostate cancer undergoing radiotherapy in combination with hormone ablation. Treatment with BCM-95 was associated with significant improvements in urinary symptoms compared to placebo, but there were no differences between groups in bowel symptoms or sexual activity. The urinary benefits correlated with increases in plasma antioxidant levels.