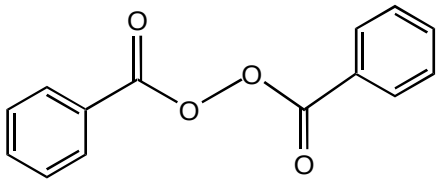
PRODUCT INFORMATION

BREVOXYL® CREAM

NAME OF THE MEDICINE
Brevoxyl contains benzoyl peroxide.

DESCRIPTION
Benzoyl peroxide is a white powder with the following chemical structure:



$C_{14}H_{10}O_4$ 242.2 94-36-0

The compound has anti-bacterial and keratolytic properties.

The formulation is a conventional cream for topical application.

Brevoxyl contains 4% benzoyl peroxide. It also contains the following excipients:
cetyl alcohol, stearyl alcohol, simethicone, propylene glycol alginate, dimethyl isosorbide, fragrance X-23304 and purified water.

PHARMACOLOGY
Benzoyl peroxide has antibacterial activity against *Propionibacterium acnes*, the organism implicated in acne vulgaris. It has keratolytic activity and is sebostatic, counteracting the hyperkeratinisation and excessive sebum production associated with acne.

Pharmacokinetic properties
The percutaneous penetration of benzoyl peroxide is concentration-dependent but relatively low, and after in vitro topical application to sections of human skin, not more than 5% of the dose penetrated through the skin. In vivo, in humans a portion of the dose absorbed dermally is almost exclusively and completely metabolised in the dermis to benzoic acid, which after entering systemic circulation, is rapidly excreted in the urine. The renal clearance of the systemically absorbed benzoic acid is so rapid that it precludes liver passage (no liver conjugates detected); therefore, systemic distribution of benzoyl peroxide and benzoic acid after dermal application of benzoyl peroxide is unlikely.

INDICATIONS
Brevoxyl is indicated for the treatment of mild to moderate acne vulgaris.

CONTRAINDICATIONS
Brevoxyl should not be used in patients with known hypersensitivity to any of the ingredients.

PRECAUTIONS
For external use only.

Contact with the eyes, eyelids, mouth, lips, other mucous membranes and broken skin should be avoided.

Care should be taken when applying the product to the neck and other sensitive areas.

Skin irritation
In normal use, a mild burning sensation will probably be felt on first application and a moderate reddening and peeling of the skin will occur within a few days. During the first weeks of treatment, a sudden increase in peeling and reddening will occur in most patients and will normally subside in a day or two if treatment is temporarily discontinued.

If excessive swelling, irritation, redness or peeling occurs, discontinue use. If these persist, consult a physician.

Excessive application will not improve efficacy, but may increase the risk of skin irritation.

Bleaching effect
This product may bleach hair and coloured or dyed fabrics. Avoid contact with hair, fabrics, furniture or carpeting.

Use with other concomitant topical acne therapy
Care should be taken when using concomitant topical acne therapy because cumulative irritancy may occur, which sometimes may be severe, especially with the use of peeling, desquamating, or abrasive agents.

If severe local irritancy occurs (e.g. severe erythema, severe dryness and itching, severe stinging/burning sensation), benzoyl peroxide should be discontinued.

Sensitivity to sunlight
Avoid excessive exposure to sunlight and other sources of ultraviolet light particularly at high altitudes or where the ground is covered. As benzoyl peroxide may cause increased sensitivity to sunlight and other sources of ultraviolet light, sunlamps should not be used and deliberate or prolonged exposure to sunlight should be avoided or minimised. Protective clothing and sunscreen should be used when exposure to sunlight cannot be avoided.

Effects on fertility
There are no data on the effect of topical benzoyl peroxide on fertility.

In a combined repeat- dose and reproduction/development toxicity study, benzoyl peroxide (250, 500 or 1,000 mg/kg/day) was administered orally to male rats for 29 days and female rats for 41-51 days. Males at 1,000 mg/kg/day showed reduced testicular and epididymal weights, but there was no effect on male fertility up to 500 mg/kg/day. Female fertility was unaffected up to 1,000 mg/kg/day; no treatment-related changes were observed in the mating time, mating rate, fertility index, number of corpora lutea and implantations. The no-observed-adverse-effect-level (NOAEL) for reproductive toxicity was considered to be 500 mg/kg/day.

Use in pregnancy (Category B2)
There are no adequate data on the topical use of benzoyl peroxide in pregnant women, thus it is not known whether dermal exposure to benzoyl peroxide during pregnancy can cause foetal harm. However, animal studies have not shown any harmful effects. In a combined repeat dose and reproduction/development toxicity study, benzoyl peroxide (250, 500 or 1,000 mg/kg/day) was administered orally to pregnant female rats. No treatment-related

changes were observed on the embryo/fetal death, fetal development and duration of pregnancy, and on the viability of the offspring, but the mean pup weight was reduced at 1,000 mg/kg/day. The NOAEL for developmental toxicity was considered to be 500 mg/kg/day.

Benzoyl peroxide should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Use in lactation

It is not known whether benzoyl peroxide or its metabolite, benzoic acid, is distributed into human breast milk. However, its pharmacokinetic properties after dermal dosing suggest that neither benzoyl peroxide nor benzoic acid is likely to be distributed systemically and thus are unlikely to be excreted in human milk.

Topical benzoyl peroxide should be used during lactation only if the expected benefit justifies the potential risk to the infant.

If used during lactation, benzoyl peroxide should not be applied to the breast area to avoid accidental ingestion by the infant.

Paediatric use

Safety and effectiveness of topical benzoyl peroxide in children under the age of 12 has not been established.

Use in the elderly

There is insufficient clinical trial data in elderly patients to provide specific recommendations for use in the elderly. Refer to adult dosing.

Carcinogenicity

Both the carcinogenicity and photocarcinogenicity of benzoyl peroxide have been extensively assessed in both mice and hamsters, by various routes of administration, in studies ranging from 12 weeks to lifetime duration. Following topical administration, benzoyl peroxide has been shown to be a tumour promoter and progression agent in a number of mice studies which utilised specific chemical tumour induction. However, benzoyl peroxide is not a carcinogen on its own, and photocarcinogenicity studies in mice showed that benzoyl peroxide does not increase the growth of tumours initiated by UV light. These limited tumour-promotion findings are not considered relevant to human dermal use, and benzoyl peroxide is considered neither carcinogenic nor photocarcinogenic when used in topical acne products at a concentration range of 2.5% to 10%.

Genotoxicity

Tested *in vitro*, benzoyl peroxide was either a weak mutagen or not mutagenic in Ames assays; it was not clastogenic in Chinese hamster lung cells, but did induce DNA damage in an unscheduled DNA synthesis test and an E.coli SOS chromotest, probably acting via generation of the reactive oxygen species. However, in humans intracellular repair mechanisms are likely to protect against such damage. Tested in vivo, benzoyl peroxide was not genotoxic in a dominant lethal mutation test in mice, in a cytogenetic assay and in a host mediated assay in rats. Overall, benzoyl peroxide is not considered to pose genotoxic risk in humans.

Effects on Laboratory Tests

None known

INTERACTION WITH OTHER MEDICINES

Concomitant application of benzoyl peroxide with tretinoin, isotretinoin and tazarotene may reduce their efficacy and increase irritation. If combination treatment is required, the products should be applied at different times of the day (e.g., one in the morning and the other in the evening).

Using topical benzoyl peroxide at the same time as topical sulfonamide or sulfone - containing products such as dapsone and sulfacetamide may cause skin and facial hair to temporarily change colour (yellow/orange).

ADVERSE EFFECTS

The following convention has been used for the classification of adverse reactions:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known* (cannot be estimated from the available data).

Clinical trial data

Skin and subcutaneous tissue disorders

Very Common:	Peeling, application site erythema
Common:	Dryness, pruritis and contact sensitisation reactions
Uncommon:	Burning sensation

Post-marketing data

General Disorders and Administration Site Conditions

Rare:	Application site discoloration and application site reactions such as irritation and pain

Immune System Disorders

Rare:	Allergic reactions, including application site hypersensitivity and anaphylaxis

Skin and Subcutaneous Tissue Disorders

Rare:	Application site rash (see also Precautions, – under the subheading Skin Irritation.

DOSAGE AND ADMINISTRATION

Apply a thin film over the whole affected area once or twice daily, preferably after washing and drying the skin. Because excessive drying of the skin may occur, the patient should start with one application daily, then increase to two times daily if needed.
If excessive dryness or peeling occurs, frequency of application should be reduced or application temporarily interrupted, per physician instruction or patient tolerability.

Maximum clinical response may be expected after approximately eight to twelve weeks of continued daily use.

Renal impairment

No dosage adjustment is necessary.

As there is very limited percutaneous absorption of benzoyl peroxide following topical application, renal impairment is not expected to result in systemic exposure of clinical significance (see Pharmacokinetics).

Hepatic impairment
No dosage adjustment is necessary.

As there is very limited percutaneous absorption of benzoyl peroxide following topical application, hepatic impairment is not expected to result in systemic exposure of clinical significance (see Pharmacokinetics).

OVERDOSAGE
Topically applied benzoyl peroxide is not generally absorbed in sufficient amounts to produce systemic effects (see Pharmacokinetics).

Excessive application may result in severe skin irritation. In this event, wash off the cream and discontinue use.

Cold compresses can provide relief from skin irritation due to excessive application.

For information on the management of excessive application or accidental ingestion of topical benzoyl peroxide, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS
Brevoxyl contains 4% w/w (40mg/g) benzoyl peroxide in a cream formulation for topical application. The product is presented in tubes containing 40g and 50g.

Not all pack sizes may be distributed in Australia.

Store below 25ºC.

NAME AND ADDRESS OF THE SPONSOR
GlaxoSmithKline Pty Ltd Consumer Healthcare Division
82 Hughes Avenue
Ermington
NSW 2115
Australia

POISON SCHEDULE OF THE MEDICINE
Unscheduled medicine.

Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG)
17 December 1996

Date of most recent amendment
20 December 2013

Version 4.0