Most patients treated with Busulfan will experience adverse effects, but the effects will differ from one patient to the next.

**ADVERSE DRUG REACTION MANAGEMENT GUIDE**

1. **Myelosuppression**
   - Busulfan may cause suppression of the blood cell production in the myeloid tissues of the bone marrow. This can result in lowering of white blood cells and platelets. It is important to have a Complete Blood Count (CBC) blood test prior to the start of each cycle of this agent. If any blood cell component is reduced below an acceptable level, the drug may need to be held until the blood cells recover. **Busulfan must NOT be dispensed** until the CBC test is completed and verified prior to each cycle of the treatment. Verification will be done by an oncology health professional.

2. **Xerostomia (dry mouth)**
   - Patients may experience xerostomia (dry mouth). This condition is characterized by a dry, tough tongue; cracks in lips and at corners of mouth; pain or burning in mouth or on tongue; sticky, dry mouth; and thick, stringy saliva. This may cause patients to have trouble speaking or swallowing, a constant sore throat, hoarseness, and dry nasal passages that may result in nosebleeds. Xerostomia can cause mouth sores, gum disease, and tooth loss. Oral candidiasis is also associated with xerostomia.

   **Prevention:** Advise patients to:
   - Check their mouth daily for red, white, or dark patches; sores or sign of tooth decay
   - Chew sugarless gum or candies to increase saliva flow
   - Avoid mouthwashes or dental products containing alcohol
   - Use a cool-mist humidifier (especially at night)
   - Sip water throughout the day or suck on ice chips
   - Drink 8 cups of water daily; eat soft, moist food; avoid alcohol, caffeinated beverages, and spicy, sugary, or acidic foods
   - Avoid smoking

   **Management:**
   - There are several OTC treatments to address xerostomia:
     - Artificial saliva (e.g. Biotène®, Moi-Stir®, Mouth Kote®)
     - Meticulous oral hygiene
       - Brush teeth 2-4 times daily with a soft bristle toothbrush. Soak toothbrush in warm water to soften bristles.
       - Floss gently once daily to avoid gum injury
       - Salt and baking soda rinses (1/2 tsp of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
Use a low-abrasive fluoride toothpaste
Avoid products that contain sodium lauryl sulfate, which may worsen canker sores
Orajel®, Vaseline®, or glycerine swabs to relieve dryness and cracks on lips and under dentures
Prescribed medications such as fluoride gel (dentist) and pilocarpine (or other drugs that increase saliva production).

3. Mucositis/Stomatitis

Stomatitis (mouth sores) is a common side effect of SUNItinib. Integrity of mucous membranes may be affected by SUNItinib treatment, leading to the swelling and reddening of membranes lining the mouth. Mouth sores or cankers may develop. Patients may complain of changes on the inner cheeks or mouth surfaces, even when mouth sores are not present or only a mild redness is evident. Patients may experience:
- Mouth pain
- Difficulty chewing
- Painful swallowing (dysphagia)

This side effect may lead to SUNItinib dosage reductions. It is important to maintain good oral health during treatment. Aggressive prevention may reduce incidence and severity of stomatitis. Treatment during stomatitis event(s) can relieve symptoms (including oral pain, oral bleeding, dental complications, soft tissue infection and dietary restrictions) and restore oral health, often within 7 to 14 days.

Prevention and Management: Good oral care is the key to prevention of stomatitis. If possible, the patient should work with their dentist (and oncologist) to correct any pre-existing dental problems before starting SUNItinib treatment. Careful and thorough oral hygiene is important, and particularly irritating foods (e.g. very spicy foods, rough textures, alcohol-containing foods or liquids) should be avoided.

Management may be achieved in many patients without prescribed therapies. Most important is meticulous oral hygiene:
- Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles
- If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®
- Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria
- Floss gently once daily to avoid gum injury
- Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
- Bland rinses, antimicrobial mouthwash (non-alcoholic)
- OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®).

If the patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips, contact the cancer care team at once and tell the patient to contact the oncology nurse or oncologist for immediate advice or a visit.
Topical preparations in widespread use for chemotherapy-induced stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. Although there is no significant evidence of the effectiveness or tolerability of these combinations, there may be a degree of symptom management (e.g. oral pain, improved ability to maintain a proper diet). Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of stomatitis resolution from chlorhexidine mouthwash, “magic” mouthwashes that contain lidocaine, and salt-and-baking soda rinses. Hydrogen peroxide may worsen mouth ulcers. In addition, mouthwash preparations containing antifungals (i.e. nystatin), broad-spectrum antibiotics, or corticosteroids have shown no benefit and possibly further worsening of stomatitis- these combinations are not recommended!

4. Rash
Rash is a common adverse effect of Busulfan. Rash symptoms often appear soon after starting treatment. This rash presents with spots and bumps on the forearms, trunk, and sometimes, the face. They are often itchy, but if scratched, may become infected and crusty. Most cases of this generalized skin rash are mild and go away on their own. Rash is more common in women and patients on higher doses, and may worsen after sun exposure. It is important to recognize rash symptoms early and start symptomatic therapy promptly.

Prevention: Prevention should begin when Busulfan therapy is begun, and continue throughout treatment. You should advise your patient to:
- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®
- Remove make-up with a gentle, skin-friendly cleanser (e.g., Neutrogena®, Dove®).
- Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide

Management: For Mild to moderate skin rash, there are some over-the-counter options you may consider:
- Antihistamine (diphenhydramine)
- Topical steroid (hydrocortisone 0.5%)
- Coal tar preparations

If the rash progresses to moderate to severe, the patient may need prescribed therapy:
- Oral corticosteroids (short course, with or without topical triamcinolone acetonide 0.1% ointment)
- Temporary interruption of therapy until the rash resolves, and then re-challenge at low dose
5. **Xerosis (Dry Skin)**
Xerosis (dry skin) occurs in some patients treated with Busulfan. Dry, scaly, itchy skin resembling atopic eczema may begin between 1 week to 3 months after starting therapy; it is persistent and often lasts several months while on continuing Busulfan treatment. This dry, scaly skin may appear on the limbs, and/or torso. It often affects the fingertips, heels, and toes. Painful fissures may develop in these areas, in nail folds, and over finger joints in excessively dry skin. This can make wearing shoes or performing tasks difficult. Dry skin may become increasingly fragile and bruise easily. Xerosis may worsen, becoming chronically red and irritable. Secondary infection with *S. aureus* may occur.

General measures to hydrate the skin and choosing the right treatment is critical to alleviating skin dryness. Frequent application of emollients that contain ammonium lactate (e.g., hydrolac or Lac-Hydrin®) or 5% to 10% urea (e.g. Eucerin® 5 or Uremol® 10) may significantly improve dryness. Instruct the patient to avoid occlusive topical creams and lotions, as they may obstruct hair follicles and thus lead to infection.

**Prevention:** Advise patients to:
- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Take short showers with warm water.
- Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®.

**Management:**
- At the first signs of skin dryness; dry skin on face, back, and chest: advise patient to switch to oil-in-water creams.
- For moderate to severe xerosis; dry skin on limbs: Use greasy water-in-oil creams or ointments.
- For eczema, recommend short-term use (1-2 weeks) of weak topical corticosteroid creams. Refer to doctor if it is not controlled by OTC treatment.
- For infection, recommend topical antibiotics. Refer to doctor if it is not controlled by OTC treatment.
- For skin fissures, treatment options include:
  - 50% propylene glycol under a plastic bandage.
  - Salicylic acid 10% ointment.
  - Colloid dressing.
  - Refer to a doctor if it is not controlled by OTC treatment.

6. **Urticaria (Hives)**
Urticaria, or hives, is a common complication from many types of drugs. Hives are itchy, red, raised wheals of various sizes and shapes. They generally last for less than 24 hours and can be very irritating to patients (who tend to scratch the hives and cause broken skin and bleeding). New lesions may continue to erupt during drug therapy. Dry skin can exacerbate hives.

**Prevention:** Advise patients to:
- Avoid over bathing, bathing in very hot water, use of harsh soaps and bubble baths. Consider showering with tepid water or adding 4 tablespoons of baking soda to bath water.
• Use tap water compresses to relieve affected skin.

Management: In addition to management of dry skin, the patient may try one or more option below:
• Use a systemic antihistamine, either an H1 blocker (e.g. diphenhydramine) or a non-sedating antihistamine (e.g. loratidine, cetirizine, desloratidine). Consider adding an H2 blocker antihistamine (e.g. ranitidine, famotidine) for chronic urticaria
• Bathing with colloidal oatmeal preparations (e.g. Aveeno®) and use of unscented moisturizing creams after bathing may help with itchiness and dry skin
• Cooling salves, such as menthol or camphor-containing products (e.g. Gold Bond®) may provide relief. Keep products in the refrigerator for additional cooling effect.
• Topical corticosteroids, beginning with OTC Hydrocortisone 0.5% cream and progressing as needed to more potent prescription corticosteroid creams, are often used
• Acetaminophen may be added to the treatment of urticarial for more painful lesions.

7. **Joint and back pain**

Patients receiving therapy often experience an aching back or pain in their joints. Patients should avoid using quinine or drinking tonic water (contains quinine). Pain may affect the leg bones, hips, and knees, and may appear in an asymmetrical pattern. Although there are no evidence-based guidelines for prevention or treatment, anecdotal reports and expert experience suggest that some patients’ pain could be eased by using mineral supplements.

**Management:** The following may provide relief from muscle aches or cramps:
• Mild pain medications- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)
• For bone or joint pain, consider the use of heating pads, ice packs, or topical arthritis creams and liniments
• Mild exercise and/or massage therapy may help reduce bone and joint pain
  • Use of a muscle relaxant may be considered (e.g. cyclobenzaprine- prescription, or acetaminophen/methocarbamol combinations-OTC)

**REFERENCES:**


Systemic Therapy Manual for Cancer Treatment, Cancer Care Nova Scotia, 2013
