



# Salviva® - Step Forward in Human Saliva Substitution

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## SUMMARY

**Introduction:** Saliva is a product of salivary glands secretion that constantly soaks - moisturizes the teeth and mucous membranes of the oral cavity. Physiological roles of saliva are: maintaining humidity, lubrication and physiological cleaning of the oral cavity, enzymatic activity (beginning of digestion), bacteriostatic and bactericidal action, prevention of dental caries.

**Topic:** The most serious health problem is the complete, permanent absence of saliva secretion, which is an absolute indication for daily use of an adequate preparation for moistening the oral cavity or saliva substitution. Salviva® is sufficiently viscous and the content that can serve as natural saliva for 4 hours. 200 ml bottle is sufficient for daily patient needs and the production costs are low (0.25 EUR per unit for laboratory level volumes, excluding primary packaging costs).

**Conclusions:** With the further innovative development of Salviva®, it is possible to apply drugs with local and systemic effects, and thus treat the patient, which opens a completely new field of application of some drugs and reduces their side effects and unpleasant effects. The quality of life of patients as well as social functionality will be significantly improved, which is very important for the working population.

**Keywords:** Saliva, Xerostomia, Dry Mouth, Medical Device

## INTRODUCTION

Saliva is a product of salivary glands secretion that constantly soaks - moisturizes the teeth and mucous membranes of the oral cavity. It is secreted by three pairs of large salivary glands: parotid, submandibular and sublingual [1],

and the latest research indicates another pair of large salivary glands of the newly discovered tubarial salivary glands. It also contains the secretion of small salivary glands, of which there are hundreds in the submucosa of the oral mu-

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cosa (mucous membrane) and some gingival crevicular fluid. About 0.5-0.6 liters of saliva is excreted daily [3]. Saliva is a complex mixture of water, ions, enzymes, glycoproteins, proteoglycans, immunoglobulins, bactericidal and other substances. The composition of saliva includes: water (96% -98%), sodium 2-21 mmol / L, potassium 10-36 mmol / L, calcium 1.2-2.8 mmol / L, magnesium 0.08-0.5 mmol /L, chlorides 5-40 mmol / L, bicarbonates 25 mmol / L, phosphates 1.4 - 39 mmol / L, mucus (composed of mucopolysaccharides and glycoproteins), antibacterial substances (thiocyanate, hydrogen peroxide), enzymes (active substances), which participate in the digestion of food in the oral cavity [4].

Physiological roles of saliva are: maintaining humidity, lubrication and physiological cleaning of the oral cavity, enzymatic activity (beginning of digestion), bacteriostatic and bactericidal action, prevention of dental caries. Saliva plays a significant role in maintaining the physiological state of the oral cavity and the initial part of the digestive tract. Glycoprotein and mucoid products, which are secreted by the salivary glands, protect the mucous membrane from potentially carcinogenic factors, such as smoking and various chemicals, and also prevent drying of the oral cavity when breathing through the mouth [4].

## TOPIC

Xerostomia - *the actual prevalence of this disorder on the general population remains controversial* [5], defined as oral dryness, occurs in mild to severe form in menopause, dehydration, anxiety, stress, electrolyte imbalance, doping in sports, dental intervention, diabetes, stroke, impaired consciousness, radiotherapy, etc. [6, 7]. The incidence of xerostomia is the highest in older adults affecting their quality of life [8]. Saliva deficiency is a relative and time-limited indication for the use of an adequate preparation for moisturizing the oral cavity or saliva replacement.

Dry mouth (xerostomia) is becoming more common in developed countries where people live longer, where polypragmatism is common. Several hundred medications can cause or exacerbate xerostomia: cytostatics, antihypertensives, antidepressants, analgesics, tranquilizers, diuretics and antihistamines, oral contraceptives [9].

The most serious health problem

is the complete, permanent absence of saliva secretion, which is an absolute indication for daily use of an adequate preparation for moistening the oral cavity or saliva substitution. Dry mouths occur: after surgical intervention of total block dissection of the neck due to advanced carcinoma, radiotherapy of the head-neck region, during and after the application of cytostatics and in Sjögren's sy. Recent research shows that natural saliva is a possible diagnostic medium for a large number of systemic diseases, i.e. that it is possible to diagnose oral cancer through markers from natural saliva, Sjögren's sy, Alzheimer's [10,11].

Reduction or complete absence of saliva also reduces the quality of everyday life. Patients with dry mouth have difficulty eating, chewing, speaking, using dentures, ulcerations of the mucous membranes, changes in the sense of taste, poor oral hygiene, inflammation of the mucous membranes, oral candida infection, progressive dental caries [12].

Remedies at hand are proper hydration; increase in humidity at night-time; avoidance of irritating dentifrices and crunchy/hard food; and use of sugar-free chewing gums/candy. Medications include mucosal lubricants, saliva replacement, and saliva stimulants as local treatment. Systemic treatment could be done with drugs: pilocarpine, cevimeline, anethole trithione, but their effect depends on the presence of functional glandular tissue and they have serious adverse effects [8,13,14].

For a successful pharmaco-therapeutic result, it is important to adequately choose the medical agent of artificial saliva, the characteristics of which depend on the indication - from moisturizer to complete substitution of saliva. The number of medical devices for maintaining oral moisture/saliva substitution is increasing on the market (Table 1a and 1b).

An absolute and permanent indication for the use of artificial human saliva is certainly the most important medical problem that needs to be solved with an adequate preparation of artificial human saliva. However, none of the existing preparations satisfies all the conditions for use immediately and permanently after surgical removal of the salivary glands within the total block dissection of the neck, in head-neck cancer: the solutions are not sterile and do not have the required retention time in the mouth. Also, if we take into account that in these cases patients need to use artificial saliva daily for the rest of their lives,

**Table 1a.** Global Competitive Overview

Source NHS 2013  
<https://www.nhs.uk/conditions/dry-mouth/>

Products available (Manufacturer)	Formulation	Prescribable by dentists on NHS?	Retail price (£)	pH	Fluoride containing?
<i>Salviva</i>	Oral Spray 250 ml	N/A	0.25 EUR per unit for laboratory level volumes, excluding primary packaging costs	Neutral	No
<i>AS Saliva Orthana</i> (AS Pharma)	Oral spray 50 mL	Yes <sup>a</sup>	£7 - £10	Neutral	Yes <sup>b</sup>
	Lozenges (30)	Yes <sup>a</sup>	< £7	Neutral	No
<i>Biotene Oralbalance<sup>e</sup></i> (GSK)	Saliva replacement gel 50 g	Yes <sup>f</sup>	£7 - £10	Acidic	No
<i>BioXtra</i> products for dry mouth (RIS Products)	Moisturising gel 40 mL	Yes <sup>a</sup>	£7 - £10	Neutral	No
	Gel mouth spray 50 mL	Yes <sup>a</sup>	£7 - £10	Neutral	Yes <sup>j</sup>
	Toothpaste 50 mL	No	< £7	Neutral	Yes <sup>k</sup>
	Mouthrinse 250 mL	No	< £7	Neutral	Yes <sup>k</sup>
<i>Glandosane</i> (Fresenius Kabi)	Aerosol spray 50 mL (lemon, neutral, peppermint)	Yes <sup>a</sup>	~ £7 <sup>l</sup>	Acidic	No
<i>Saliveze</i> (Wyvern)	Oral spray 50 mL	Yes <sup>a</sup>	< £7	Neutral	No
<i>Saliva Stimulating Tablets (SST)</i> (Medac)	Tablets (100)	Yes	£7 - £10	Acidic <sup>m</sup>	No
<i>Xerotin</i> (SpePharm)	Oral spray 100 mL	Yes <sup>n</sup>	> £7 <sup>o</sup>	Neutral	No
<i>XyliMelt</i> (1-4h, 4-8h sleeping)	Discs	Yes	\$10	Alkaline	

**Table 1b.** Global Competitive Overview

Source NHS 2013  
<https://www.nhs.uk/conditions/dry-mouth/>

Products available (Manufacturer)	Formulation	Animal derived ingredients?	Gluten free?	Sugar free?	Paraben free?
<i>Salviva</i>	Oral Spray 250 ml	No	Yes	Yes	Yes
<i>AS Saliva Orthana</i> (AS Pharma)	Oral spray 50 mL	Yes <sup>c</sup>	Yes	Yes	No
	Lozenges (30)	Yes <sup>c</sup>	Yes	Yes <sup>d</sup>	
<i>Biotene Oralbalance<sup>e</sup></i> (GSK)	Saliva replacement gel 50 g	Yes <sup>g</sup>	Yes	Yes <sup>h</sup>	No
<i>BioXtra</i> products for dry mouth (RIS Products)	Moisturising gel 40 mL	Yes <sup>i</sup>	Yes	Yes	No
	Gel mouth spray 50 mL	Yes <sup>i</sup>	Yes	Yes	No
	Toothpaste 50 mL	Yes <sup>i</sup>	Yes	Yes	No
	Mouthrinse 250 mL	Yes <sup>i</sup>	Yes	Yes	No
<i>Glandosane</i> (Fresenius Kabi)	Aerosol spray 50 mL (lemon, neutral, peppermint)	No	Yes	Yes <sup>d</sup>	Yes
<i>Saliveze</i> (Wyvern)	Oral spray 50 mL	No	Yes	Yes	Yes
<i>Saliva Stimulating Tablets (SST)</i> (Medac)	Tablets (100)	No	Yes	Yes <sup>d</sup>	Yes
<i>Xerotin</i> (SpePharm)	Oral spray 100 mL	No	Yes	Yes <sup>d</sup>	Yes
<i>XyliMelt</i> (1-4h, 4-8h sleeping)	Discs	No	Yes	Yes	Yes

the economic aspect becomes very important.

As part of the academic Innovative Project of the Ministry of Education, Science and Technology of the Republic of Serbia, a research team from Belgrade produced Salviva® artificial human saliva [15]. The Salviva®, medical device, is also in the application procedure as a new technological solution within the nomenclature of the Ministry of Education, Science and Technological Development of the Republic of Serbia, so this paper does not state the exact composition of the product. The main goal of our project is to find artificial saliva that, in terms of its characteristics, most closely matches natural saliva, and can be used for the purpose of substitution according to indications. Physicochemical tests of IP Salviva® were performed in the laboratory of the Innovation Center of the Faculty of Technology and Metallurgy, University of Belgrade. The target group of users of the results of this innovative project are all patients with malignant tumors of the region - head and neck Sjögren's syndrome, conditions with a reduced amount of natural saliva: menopause, dental prosthetic works, use of drugs of certain categories. The logical aspiration is to provide these people with functionality and quick recovery through help in realizing and improving the ability to chew, swallow, speak, laugh. The use of Salviva® is simple, harmless, and very useful: it enables patients the physiological function of chewing, speech and tissue recovery after invasive treatments through direct substitution. Its composition is compatible with natural saliva, there are no preservatives and other additives and there is no possibility of allergic and toxic effects. With the innovative development of Salviva®, it is possible to apply drugs with local and systemic effects, and in this way treat the patient, which opens a completely new form of some drugs and reduces their side effects (cytostatics, antibiotics, monoclonal antibodies). The quality of life will be significantly improved, as well as social functionality, which is very important for the working population.

The medical devices currently available on the market do not have a precise retention time on the oral mucosa, and Salviva® maintains the moisturizing effect for 4 hours. Tests of biocompatibility (does not cause irritation, can be used immediately after surgery, during radiotherapy, during cytostatic therapy), sterility (can be used immediately after surgery) and apyrogenicity have given excel-

lent results. The preparation meets the highest standards of microbiological correctness and apyrogenicity, which is confirmed by the results of analyzes from accredited laboratories of the Military Medical Academy in Belgrade and the Torlak Vaccine Institute in Belgrade. This is very important in the postoperative course of the patient's recovery. The epidemiological data about diseases / health conditions indications for Salviva® indicate that solving this health problem is very important [16].

Aimed at satisfying the unmet need for a product that serves as an effective saliva replacement in xerostomia (dry mouth), especially caused by neck and head cancer and resulting resection, damage or disease of salivary glands, where treatments like pilocarpine and other salivary stimulants are ineffective.

Current options in Serbia, such as Hartmann solution, are ineffective due to lack of viscosity.

Salviva® is sufficiently viscous and the content that can serve as natural saliva for 4 hours. Bottle of 200 ml is sufficient for daily patient needs and the production costs are low (0.25 EUR per unit for laboratory level volumes, excluding primary packaging costs).

#### Technical Details:

- Product is categorized as II-A Medical Device;
- Shelf life – 6 months (or one month after opening);
- Following tests conducted:
  - Sterility (6 months);
  - Apyrogenicity (6 months);
  - Primary cutaneous irritations test in hamsters (6 months);
  - Sensibilization;
  - In vitro cytotoxicity test.

#### Product Characteristics:

- Competitive pricing possible;
- 4 hours of moisturizing effect;
- pH neutral;
- No preservatives (paraben free);
- No relevant competition in Serbia nor regionally (500 ml Hartmann solution is not a comparable product, but is being used for this purpose and costs around 1.1 EUR in retail setting);
- Product can be further developed through addition of drugs/antibiotics.

**Market Size:**

- Indicated for partial or complete saliva substitution in:
  - 1) Neck area irradiation;
  - 2) Postoperative conditions – Total or partial dissection of the neck;
  - 3) Chemotherapy;
  - 4) Mumps;
  - 5) Syndromes – Sjögren, Riley-Day, Plummer Vinson, Heerfordt;
  - 6) Diabetes;
  - 7) Prosthetic interventions;
  - 8) Heavy metals or drugs intoxication;
  - 9) Cerebral coma;
  - 10) Drug use (atropine, antidepressants, anti-histamines);
  - 11) Menopausal xerostomia;
  - 12) Dehydration, anxiety, etc.

**CONCLUSION**

Understanding of saliva and its role in oral health will help promote awareness among health care workers regarding the problems arising when the quantity or quality of saliva is decreased; this awareness and understanding is important to the prevention, early diagnosis and treatment of the condition.

The Salviva® product is the result of this Innovation Project and is unique in our market, and competitive in the foreign market, a substitute-type preparation for human saliva (Picture 1), by establishing a simple economically viable aseptic manufacturing technology.

The preparation meets the highest standards of microbiological correctness and apyrogenicity, which is confirmed by the results of analyzes from accredited laboratories of the Military Medical Academy in Belgrade and the Torlak Vaccine Institute in Belgrade.

With the further innovative development of Salviva®, it is possible to apply drugs with local and systemic effects, and thus treat the patient, which opens a completely new field of application of some drugs and reduces their side effects and unpleasant effects.

The quality of life of patients as well as social functionality will be significantly improved, which is very important for the working population.

The price of Salviva® is significantly lower than existing products, and the economic profitability is at a high level.

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**CONFLICT OF INTEREST**

All authors declare that they have no conflict of interest.

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Picture 1. The Salviva®



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## Salviva® - korak napred u supstituciji humane pljuvačke

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### KRATAK SADRŽAJ

**Uvod:** Pljuvačka je proizvod sekrecije pljuvačnih žlezda koji se konstantno luči - vlaži zube i sluznicu usne šupljine. Fiziološke uloge pljuvačke su: održavanje vlažnosti, podmazivanje i fiziološko čišćenje usne šupljine, enzimska aktivnost (početak varenja), bakteriostatsko i baktericidno delovanje, prevencija zubnog karijesa.

**Tema:** Najozbiljniji zdravstveni problem, koji predstavlja apsolutnu indikaciju za svakodnevnu upotrebu adekvatnog preparata za vlaženje usne šupljine ili supstituciju pljuvačke, je potpuno, trajno odsustvo lučenja pljuvačke. Salviva® je dovoljno viskoznan proizvod koji sadrži sve komponente da može poslužiti kao prirodna pljuvačka tokom četiri sata. Bočica od 200 ml je dovoljana za dnevne potrebe pacijenta, a proizvodni troškovi su niski (0,25 EUR po jedinici za laboratorijske količine, isključujući troškove primarnog pakovanja).

**Zaključak:** Daljim razvojem Salvive®, moguće je primeniti lekove sa lokalnim i sistemskim delovanjem, a samim tim i lečiti pacijenta, što otvara potpuno novo polje primene određenih lekova i smanjuje njihove neželjene i neprijatne efekte. Kvalitet života pacijenta kao i socijalna funkcionalnost biće značajno unapređeni, što je veoma važno za radno sposobnu populaciju.

**Cljučne reči:** saliva, pljuvačka, kserostomija, suva usta, medicinsko sredstvo

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