LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fludent Hallon
0.25 mg lozenges

(Sodium fluoride)

Asp.no 2006-1376

This module reflects the scientific discussion for the approval of Fludent Hallon 0.25 mg lozenges. The procedure was finalised at 2008-04-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Actavis Group hf has applied for a marketing authorisation for Fludent Hallon 0.25 mg lozenges. The active substance sodium fluoride is the same as in Fludent, lozenges marketed by Actavis Group hf since 1975. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Fludent Hallon is presented in the form of lozenge containing sodium fluoride which corresponds to 0,25 mg fluoride. The excipients are sorbitol, xylitol, povidone, macrogol 6000, raspberry flavour, talc and magnesium stearate. The lozenges are packed in HDPE containers with tamper evident closure of PE.

II.2 Drug Substance

Sodium fluoride has a monograph in the Ph Eur.
Sodium fluoride is a white powder or colourless crystals, soluble in water and practically insoluble in alcohol. The structure of sodium fluoride has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.
The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.
Stability studies have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Fludent Hallon is formulated using excipients described in the current Ph Eur, except for the raspberry flavour which is controlled according to acceptable in house specifications. The raspberry flavour is stated to be of Food Grade Quality and comply with Directive 88/388/EEC. All raw materials used in the product are of vegetable origin.
The product development has taken into consideration the physico-chemical characteristics of the active substance.
The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with the storage restriction, do not store above 30°C.

III. NON-CLINICAL ASPECTS

The drug substance fluoride is a well known ion and its toxicity profile in human is known. The excipients are also established compounds. There is no non-clinical concern with the use of Fludent Hallon at recommended dosage.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fludent, lozenges has been marketed in Sweden and several other European and non-European countries for more than twenty years. It is used in patients above three years of age with high activity of dental caries and/or enhanced risk for dental caries.

IV.2 Pharmacodynamics

The effect of fluoride is mainly local, fluoride concentrated in plaque and saliva inhibits the demineralization of sound enamel and enhances the remineralization of demineralized enamel. Fluoride is released from dental plaque in response to lowered pH at the tooth-plaque interfaces, resulting from the methabolic activity of cariogenic bacteria. The released fluoride and the fluoride present in saliva are then taken up, along with calcium and phosphate, by de-mineralized enamel to establish an improved enamel crystal structure. This improved structure is more acid resistant and contains more fluoride and less carbonate. Fluoride is more readily taken up by demineralized enamel than by sound enamel. Fluoride also inhibits dental caries by affecting the metabolic activity of cariogenic bacteria.

IV.3 Clinical efficacy

Dental caries (i.e., tooth decay) is an infectious, multifactorial disease afflicting most persons in industrialized countries and some developing countries. Fluoride's ability to inhibit or even reverse the initiation and progression of dental caries is well documented. Much of the research demonstrating the efficacy and effectiveness of individual fluoride modalities in preventing and controlling dental caries was conducted before 1980. The use of fluoride for preventing progression of dental caries and healing initial caries lesions is well established and recommended by international societies and guidelines. The lozenge stimulates saliva excretion and enhances the concentration of fluoride ions in the saliva. In persons at low risk to develop dental caries, limited benefit is gained by adding extra fluoride besides using fluoride tooth-paste. On the other hand, persons at high risk for dental caries might require additional fluoride administration, such as fluoride lozenges, to reduce development of caries. It is recommended specifically patients suffering from dry mouth (decreased saliva production), wearing loose denture, or braces.

IV.4 Clinical safety

Fluoride ingested during tooth development can result in a range of visually detectable changes in enamel opacity (white patches at or below the surface) because of hypomineralization. These changes have been broadly termed enamel fluorosis, which can be cosmetically objectionable. Severe forms of this condition can occur only when young children ingest excess fluoride, from any source, during critical periods of tooth development. The occurrence of enamel fluorosis is reported to be most strongly associated with cumulative fluoride intake during enamel development, but the severity of the condition depends on the dose, duration, and timing of fluoride intake. The transition and early maturation stages of enamel development appear to be most susceptible to the effects of fluoride, these stages occur at varying times for different tooth types. Enamel is no longer susceptible once its preeruptive maturation is complete, thus concerns regarding the risk for enamel fluorosis are limited to children aged ≤8 years. In order to reduce the risk for enamel fluorosis, children below 7 years should not receive more than 0.75 mg fluoride (3 lozenges) per day, and children 7-12 year should not receive more than 1 mg fluoride (4 lozenges) per day.

Acute lethal toxicity is calculated to 5 g for adults and 33 mg/kg for children. A 2 gram dose to an adult lead to severe intoxication, while up to 110 mg to children above 1 year (equal to 200

tablets á 0.25 mg fluoride), did not lead to intoxication. Symptoms of intoxication include tremor, paraesthesiae, CNS depression, seizures and shock.

IV.5 Discussion on the clinical aspects

The benefit – risk profile of Fludent lozenges is considered positive when used according to the dosage regimen stated in the SPC.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Fludent Hallon 0.25 mg lozenges is recommended for approval.

VI. APPROVAL

Fludent Hallon 0.25 mg lozenges was approved in the national procedure on 2008-04-18.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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