1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

STEDMAN

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

STEDNAC Gel (Aceclofenac, Linseed Oil, Methyl Salicylate and Menthol Gel)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

Aceclofenac BP 1.5% w/w
Linseed Oil BP 3.0% w/w
(containing Alpha Linolenic Acid)
Methyl Salicylate BP 10.0% w/w
Menthol USP 5.0% w/w
Benzyl Alcohol BP 1.0% w/w
(as preservative)
Gel base q.s
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM:

Topical Gel

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications

Stednac Gel is indicated for local application for relief of pain and inflammation associated with acute musculoskeletal pain in adults like backache, arthritis, strains, sprains etc.

4.2 Posology and method of administration

Apply on the affected area daily 3-4 times or as directed by the physician. Do not rub vigorously.

4.3 Contraindications

Stednac gel is contraindicated in those individuals with known hypersensitivity to Aceclofenac, Linseed Oil, Methyl Salicylate, Menthol and Benzyl Alcohol or the other ingredients in the gel.

Stednac Gel is also contra indicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

4.4 Special warnings and precautions for use

Stednac Gel should be applied only to intact, healthy skin and not to skin wounds, infections, exudative dermatoses or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should never be taken by mouth.

Stednac Gel is “For external use only”. Avoid getting in eyes or on broken or irritated skin. If condition worsens, or if symptoms persist for more than 28 days in the case of arthritis (14 days with post-herpetic neuralgia), or clear up and occur again within a few days, discontinue use of this product and consult your doctor. Keep out of reach of children.

The likelihood of systemic side effects occurring following topical Aceclofenac is small compared with the frequency of side effects following oral Aceclofenac. However, when Stednac Gel is applied to relatively large areas of skin and over a prolonged period of time, the possibility of systemic side effects cannot be excluded. In general, topical NSAID’s should be used with caution in those patients with a history of (or active) gastro-intestinal ulceration or bleeding, or severe renal impairment.

4.5 Interaction with other medicinal products and other forms of Interactions

The concurrent use of NSAID’s and warfarin has been associated with severe, sometimes fatal, hemorrhage. The exact mechanism of the interaction between NSAID’s and warfarin is unknown, but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAID’s. Systemic reactions are unlikely to occur when Stednac Gel is used as recommended. Nevertheless, the possibility of such an interaction should be borne in mind.

4.6 Pregnancy and lactation

In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some fetuses.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

Local Reactions

Occasional: allergic or non-allergic contact dermatitis (with symptoms and signs such as itching, reddening, edema, papules, vesicles, bullae, or scaling of the skin).

Salicylate intoxication can occur after ingestion or topical application of Methyl Salicylate.

Systemic Reactions

In isolated cases: generalized skin rash; hypersensitivity reactions (e.g. asthmatic attack, angioedema), or Photosensitivity reactions.

4.9 Overdose

The low systemic absorption of ingredients in Stednac Gel renders overdosage extremely unlikely. In the event of accidental ingestion, resulting in significant systemic side-effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory drugs should be used.

Like other salicylates, methyl salicylate may be absorbed through intact skin. Percutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin. The amount absorbed will also be increased by application to large areas of skin.

Results from a study in healthy subjects showed that a considerable amount of salicylic acid may be absorbed through the skin after topical application of products containing methyl salicylate.

Both the rate and extent of absorption increased after repeated application; the bioavailability of the ointment preparation used in the study increased from 15% after the second dose to 22% after the third to eighth dose. The authors recommend that topical analgesic preparations containing methyl salicylate or other salicylates should be used with caution in patients at increased risk of developing salicylate adverse effects.

Results from another study showing high tissue to plasma ratios after topical application of a methyl salicylate formulation suggest that direct penetration and not recirculation in the blood is responsible for the salicylate concentrations found. The results also showed that methyl salicylate is extensively metabolised to salicylic acid in the dermal and subcutaneous tissues after topical application.

Management of overdosage essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from Stednac Gel overdosage. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Aceclofenac

Aceclofenac is a new generation non-steroidal anti-inflammatory drug showing effective anti-inflammatory and analgesic properties.

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins.

The Drugs inhibits synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor and prostaglandin E_2 (PGE2) production. Effects on cell adhesion molecular from neurophils have also been noted. In vitro data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by aceclofenac in whole blood assays, with selectivity for Cox-2 being evident.

Aceclofenac has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1 activity. In vitro data indicate stimulation by the drug of synthesis of glycosaminoglycan in osteoarthritic cartilage. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyacelofenac has chondroprotective properties attributable to suppression of IL-1 mediated promatrix metalloproteinase production and proteoglycan release.

Aceclofenac is a novel NSAID known to exhibit multifactor mechanism of action. Aceclofenac was developed in order to provide a highly effective pain relieving therapy with a reduced side effect profile.

1. Aceclofenac directly blocks PGE 2 secretion at the site of inflammation by inhibiting IL-Beta & TNF in the inflammatory cells (Intracellular Action). Aceclofenac has been demonstrated to inhibit cyclooxygenase (COX) activity and to suppress the PGE 2 production by inflammatory cells, which are likely to be a primary source of PGE 2. Inflammatory cells release IL-1 and

2. TNF, which produce PGE 2 by induction of COX-2. Aceclofenac and 4`-hydroxyaceclofenac penetrate the inflammatory cells like polymorphonuclears, monocytes and rheumatoid synovial cells and get hydrolyzed to the active metabolites diclofenac and 4`-hydroxydiclofenac which inhibit IL-1 and TNF released by the inflammatory cells and therefore suppress production of PGE 2 at the site of inflammation.

3. Aceclofenac stimulates the synthesis of the extracellular matrix of the Human Articular Cartilages.

Aceclofenac blocks degeneration and stimulates synthesis of extracellular matrix of cartilages by inhibiting the action of different cytokines. Aceclofenac and the metabolites inhibit IL-6 production by human chondrocytes. This leads to inhibition of increase of inflammatory cells in synovial tissue, inhibition of IL-1 amplification, inhibition of increased MMP synthesis and thus ensuring proteoglycan production. Aceclofenac also inhibits IL-1 and TNF production by human chondrocytes, inflammatory cells and synovial cells and therefore blocks suppression of GAG and collagen synthesis and stimulates growth factor mediated synthesis of GAG and collagen. 4`-hydroxyaceclofenac, a metabolite of aceclofenac inhibits pro MMP1 and

pro MMP3 produced by synovial cells (Rheumatoid Synovial Cells) in serum and in synovial fluid and thus inhibits progressive joint destruction by MMPs.

4. Aceclofenac inhibits Neutrophil Adhesion & Accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of Neutrophils.

Importance of aceclofenac as a NSAID has inspired development of topical dosage forms. This mode of administration may help avoid typical side effects associated with oral administration of NSAIDs, which have led to its withdrawal. Furthermore, aceclofenac topical dosage forms can be used as a supplement to oral therapy for better treatment of conditions such as arthritis.

Linseed Oil

Linseed oil is used in veterinary medicine as a purgative for horses and cattle. In man, linseed oil is included in topical preparations for a variety of skin disorders. It has been tried as a vegetable source of omega-3 fatty acids. **(Martindale 36th edition P.2334).** Linseed oil may have anti-inflammatory, anti-thrombotic and anti-proliferative activities. It is a very rich source of alpha-linolenic acid. Alpha-linolenic acid concentration in flaxseed oil ranges from approximately 40 to 60%. ALA is metabolized to eicosopentaenoic acid (EPA). EPA is a precursor of the series-3 prostaglandins, the series-5 leukotrienes and the series-3 thromboxanes. These eicosanoids have anti-inflammatory and anti-atherogenic properties. ALA metabolites may also inhibit the production of the pro-inflammatory eicosanoids, prostaglandin E2 (PGE2) and leukotriene B4 (LTB4), as well as the pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1 beta). Incorporation of ALA and its metabolites in cell membranes can affect membrane fluidity and may play a role in anti-inflammatory activity, inhibition of platelet aggregation and possibly in anti-proliferative actions of ALA.

Methyl Salicylate

Methyl Salicylate is a counter irritant. It has been shown that esterases present in the skin rapidly hydrolyze Salicylate esters to release the active Salicylate in both the epidermis and dermis. Methyl Salicylate produces a paradoxical pain relieving effect by producing a sensation that counters more intense feeling of pain (gate control theory). The pleasant smell of methyl Salicylate is always associated with pain relief.

Menthol

Menthol, an alcohol obtained from diverse mint oils in low concentrations stimulates the sensory nerve endings for cold and hence causes a sensation of coolness. Local analgesic effect also accompanies this effect. In addition menthol has been shown to enhance the skin penetration of methyl Salicylate and to inhibit the in vivo and in vitro hydrolysis of methyl Salicylate to salicylic acid.

Benzyl alcohol

Benzyl alcohol is used as an antimicrobial preservative. It is bacteriostatic mainly against Gram-positive organisms and some fungi. It is used in a range of pharmaceutical preparations in concentrations up to 2%. Concentrations of 5% or more are employed when it is used as a solubiliser. Benzyl alcohol is used as a preservative in foods and cosmetics. It is also used as a disinfectant at a concentration of 10%. In addition to its antiseptic properties, concentrations of benzyl alcohol of up to 10% possess weak local anaesthetic and antipruritic activity. **(Martindale 36th edition P.1632)**

5.2 Pharmacokinetic properties

NSAIDs administered topically penetrate slowly and in small quantities into the systemic circulation; bioavailability and maximal plasma NSAID concentration after topical application are generally less than 5 and 15%, respectively, compared with equivalent oral administration. Product formulation may have a dramatic impact, not only on absorption rates but also on penetration depth.

Compared with oral administration, topical application leads to relatively high NSAID concentrations in the dermis. Concentrations achieved in the muscle tissue below the site of application are variable, but are at least equivalent to that obtained with oral administration. NSAIDs applied topically do reach the synovial fluid, but the extent and mechanism (topical penetration versus distribution via the systemic circulation) remain to be determined. In addition, marked interindividual variability was noted in all studies; percutaneous absorption may be strongly influenced by individual skin properties.

In general, interpretation of clinical studies measuring efficacy of topical NSAIDs in rheumatic disease states is difficult because of a remarkably high placebo response

rate, use of rescue paracetamol (acetaminophen), and significant variability in percutaneous absorption and response rates between patients.

Overall efficacy rates attributable to topical NSAIDs in patients with rheumatic disorders ranged from 18 to 92% of treated patients. Topically applied NSAIDs have a superior safety profile to oral formulations. Adverse effects secondary to topical NSAID application occur in approximately 10 to 15% of patients and are primarily cutaneous in nature (rash and pruritus at site of application). GI adverse drug reactions are rare with topically applied NSAIDs, compared with a 15% incidence reported for oral NSAIDs. Available clinical studies suggest, but do not document, equivalent efficacy of topical over oral NSAIDs in rheumatic diseases.

In humans approximately 12 to 20% of topically applied methyl salicylic acid is systemically absorbed within 10 hours of application. When methyl salicylic acid was given orally to 6 healthy adults, about 21% of unhydrolysed ester was present in plasma after 90 minutes. In a case of an accidental oral intake of wintergreen oil 21% was present in the circulation after 1.5 hours.

Pharmacokinetic study of Aceclofenac Gel

In vitro studies: In vitro diffusion studies for all formulations were carried out using a Keshary-Chein (KC) type diffusion cell (4, 5).

The diffusion cell apparatus was fabricated locally as an open-ended cylindrical tube with a 3.7994 cm2 area and 100 mm height, having a diffusion area of 3.8 cm2. Twenty percent (*V*/*V*) acetic acid was used as receptor medium. A weighed quantity of the formulation equivalent to 25 mg of the drug was placed onto the dialysis membrane-70 (Himedia Laboratories Ltd., India) and was immersed slightly in 20 mL of receptor medium which was continuously stirred and maintained at 37 ± 1 °C. Aliquots of 2.0 mL were withdrawn at specific time intervals up to 6 h. From the withdrawn aliquot, 1.0 mL was transferred into a 100-mL volumetric flask, suitably diluted and the AF content was estimated spectrophotometrically.

Average of three determinations was used to calculate the cumulative percent drug release at each time point.

In vitro skin permeation studies were carried out for the best three formulations that exhibited higher drug release through the dialysis membrane-70 (4, 5) using rat

abdominal skin. Rat skin was obtained from the abdominal portion of an albino rat after sacrificing the animal. The hair and fat were removed after treating the skin with 0.32 mol L–1 ammonia solution for 30 minutes. The skin was tied to the KC diffusion cell (donor cell) so that the stratum corneum side of the skin was in intimate contact with the release surface of the formulation in the donor cell. All experiments were carried out in triplicate.

Kinetic analysis of release and skin permeability data. – The release and skin permeability data of the best three semisolid formulations were subjected to kinetic analysis to establish the drug release mechanism. The release data were fitted to the zero-order, first- -order and matrix (Higuchi model) equations (6, 7).

Skin irritation test. – The draize patch test was used on rabbits to evaluate the irritation potential of the selected topical formulations. White New Zealand rabbits of either sex (2.75 ± 0.25 kg, 8–9 weeks) were supplied by Singhla Scientific suppliers, Ambala, India, and were housed individually in the animal house with food and water given *ad libitum* (8).

Rabbits were divided into three groups (n = 3): group 1 – no application (control), group 2 – placebo semisolid topical base without AF, and group 3 – formulation treated. The back of the rabbits was clipped free of hair 24 h prior to the formulation application. The formulation, 0.5 g, was applied on the hair-free skin of rabbits by uniform spreading over an area of 4 cm2. The skin surface was observed for any visible change such as erythema (redness) after 24, 48 and 72 h of the formulation application. The mean erythemal scores were recorded depending on the degree of erythema:

no erythema = 0,

slight erythema (barely perceptible – light pink) = 1,

moderate erythema (dark pink) = 2,

moderate to severe erythema (light red) = 3, and

severe erythema (extreme redness) = 4 (8).

Analgesic and anti-inflammatory activity. – Analgesic and anti-inflammatory activities of selected formulations were evaluated using male Wistar rats (210 ± 10 g, 6–8 weeks) by carrageenan-induced thermal hyperalgesia using the procedure described by Padi *et al*. (9) and the paw edema method using a mercury plethysmograph as

described by Winter *et al*. (10), respectively. For this purpose, rats were divided into four groups (*n* = 6):

group 1 – control (no treatment), group 2 – AF2 treated, group 3 – AF3 treated and group 4 – AF7 treated. They were housed individually with food and water given *ad libitum*.

Linseed oil

Linseed consists of the dried, ripe seeds of Linum usitatissimus L. (26).

The seeds contain nearly 25 % of bulk materials (3 – 6 % of mucilage, 4 – 7 % of alimentary fibres), 30 – 45% fatty oil, 20 – 27 % proteins, 3 – 5 % minerals, vitamins, lignan percursors, linustatin, neolinustatin and linamarin, enzymes. The content of water is 5 – 14 % (16, 22, 80).

Methyl salicylate

Like other salicylates, methyl salicylate may be absorbed through intact skin. Percutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin. The amount absorbed will also be increased by application to large areas of skin.

Menthol

After absorption, menthol is excreted in the urine and bile as a glucuronide.

Absorption The systemic absorption of camphor, menthol, and methyl salicylate from dermal patches containing all three ingredients has been studied. The absolute bioavailability of these compounds could not be determined from this study, but there did not appear to be any substantial systemic accumulation even after unrealistically high exposure for prolonged periods.

1. Martin D, *et al.* Dermal absorption of camphor, menthol, and methyl salicylate in humans. *J Clin Pharmacol*. 2004; 44: 1151–7.

Benzyl Alcohol

Benzyl alcohol is metabolised to benzoic acid. This is conjugated with glycine in the liver to form hippuric acid which is excreted in the urine. Benzaldehyde and benzoic acid are degradation products *in vitro*.

5.3 Preclinical safety data

Toxicity & Carcinogenicity:

Toxicological studies have not been performed. Percutaneous absorption of active ingredients of topical formulations like Stednac gel occurs in sufficient amounts to achieve therapeutic levels in target tissues only and hence concentration in plasma to cause systemic toxicity and thereby other serious adverse effects is comparably low. In some cases it may produce mild or moderate irritation, redness and pruritus which remit on interruption of the treatment.

Twice daily topical application of a cream containing Aceclofenac produces acute eczema in the sun exposed area of leg. It gives a proof to its photosensitivity.

Systemic reactions, particularly gastrointestinal disturbance and asthma are quite rare.

Sub-Chronic Toxicological Evaluation of Aceclofenac In Rats

Non-steroidal anti-inflammatory drugs (NSAIDs) are mixed group of compounds that differ in chemical structure but share similar pharmacological action. Aceclofenac is NSAID used for relief of pain and inflammation in osteoarthritis, rheumatid arthritis and ankylosing spondylitis. Whenever aceclofenac is administered into the biological system, different types of interaction occur resulting into different dose related responses. In most cases these responses are desired and useful, but there are number of other effects which are not advantageous. The objective of the present study was to evaluate the sub-chronic toxicity study of aceclofenac in wistar rats (male and female), at different dose levels, ranging from 5 to 20 mg/kg body weight. Various physiological, hematological, biochemical parameters were studied and found not to be changed significantly. Aceclofenac did not show any significant behaviors toxicity except some sort of irritability in high and middle dose.

Aceclofenac is an effective simple analgesic and antipyretic drug. Aceclofenac has been proven to be more superior to paracetamol and naproxen in pain reduction and functional improvement in symptomatic patients with osteoarthritis of knee, with no significant difference in tolerability.

In the present investigation, there were no signs of local injury and inflammatory response at site of injection in the treated group of rats. No behavioral changes were observed during the study period in all the treatment groups. Blood was evaluated for hematological toxicity of aceclofenac infusion. Hemogram was estimated and no deleterious effects were observed on blood cell count, hemoglobin and other related parameters. Liver is the vital organ which is involved in the maintenance of metabolic

function and detoxification of drugs. Liver damage is associated with cellular necrosis, increase in liquid tissue peroxidation and depletion in the tissue GSH levels. In addition, serum levels of many biochemical markers like SGOT, SGPT, BUN and total serum protein levels are elevated.

At the termination of day 29, all biochemical parameters studied i.e. total serum protein, SAP, BUN and blood sugar were found to be comparable with controls and were within the normal biological and laboratory limits but SGPT, SGOT value was high in case of high and middle dose treated animals. In the present study, biochemical parameters related to kidney function were observed in blood urea, creatinine, glucose and proteins with respect to control. Organ weight analysis showed no change in the weights of organs of rats of different dose groups as compared to control.

There were no signs of significant toxicity observed in any of the organ in histopathological analysis. Thus histological studies provide support to the safety data of other physiological, biochemical and hematological parameters of aceclofenac infusion at low dose. However, after dissection of high dose animals the stomach showed hyperemic patchy areas mainly in the antral region.

At the middle doses (10 mg/kg) all animals showed same signs of toxicity during same duration but no mortality was found whereas at 5 mg/kg no significant toxicity was found. It was observed that 4 animals out of 12 (6male and 6 female) have died at high dose of 20 mg/kg after 12 days of administration of drugs. With this dose (20 mg/kg) animals showed bleeding per rectum as well as black stool.

In general the extensive studies of efficacy and toxicity of drugs by the topical route are very limited.

Human Toxicity Excerpts:

The lethal dose of methyl salicylate is considerably less than that of sodium salicylate. As little as 4 ml (4.7 g) of methyl salicylate may be fatal in children. /methyl salicylate/ [gilman, a.g., t.w. rall, a.s. nies and p. Taylor (eds.). Goodman and gilman's the pharmacological basis of therapeutics. 8th ed. New york, ny. Pergamon press, 1990. 651]**peer reviewed**

When ingested, the highly concentrated liquid methyl salicylate in the form of wintergreen oil, as with other volatile oils, can induce vomiting and is a notorious source for severe, often fatal poisonings.

Methyl salicylate was found to be negative when tested for mutagenicity using the Salmonella/microsome preincubation assay, using the standard protocol approved by the National Toxicology Program (NTP). Methyl salicylate was tested in as many as 5 Salmonella typhimurium strains (TA1535, TA1537, TA97, TA98, and TA100) in the presence and absence of rat and hamster liver S-9, at doses of 1,000, 3,300,10,000, 33,300, 100,000, and 333,300 ug/plate. The highest ineffective dose tested in any Salmonella typhimurium strain was 333,000 ug/plate.
[Mortelmans K et al; Environ Mutagen 8: 1-119 (1986)]**PEER REVIEWED**
Methyl salicylate (MS) is teratogenic in animals and can be absorbed in toxic quantities by the dermal route. Consequently the dermal absorption and teratogenic potential of a petroleum-based grease (PBG) manufactured using methyl salicylate (3%) was assessed.
The test material (petroleum based grease/methyl salicylate) was dermally applied at doses of either 0, 1, 3, or 6 g/kg/day to groups (N greater than or equal to 12) of pregnant rats on gestational days 6-15. Undiluted methyl salicylate was applied to the positive control group at a dose of 2 g/kg/day and was reduced to 1 g/kg/day on gestational days 10-15 due to maternal toxicity (ie, 25% mortality and severe dermal irritation). Positive control animals evidenced a 100% incidence of total resorptions. Urinalysis revealed very high concentrations of salicylic acid in the positive controls and that a significant proportion of the available methyl salicylate was absorbed from the petroleum based grease/methyl salicylate test material. However, the urinary concentrations of salicylic acid in petroleum based grease/methyl salicylate treated animals were far below the toxic levels observed in methyl salicylate treated animals.

Despite the high doses of petroleum based grease/methyl salicylate, there were no signs of maternal toxicity (as measured by food consumption and body weight parameters or clinical signs) and no alterations in reproductive parameters. Fetal external and visceral examinations revealed no malformations or variations that were related to petroleum based grease/methyl salicylate treatment.

These findings confirm the developmental toxicity of methyl salicylate and indicate that petroleum based grease/methyl salicylate was not a teratogenic hazard under these test conditions. The maternal and developmental No-Observable-Adverse-Effect-

Level for petroleum based grease/methyl salicylate was greater than 6 g/kg/day. **[Infurna R et al; Teratology 41 (5): 566 (1990)]**PEER REVIEWED****

Prenatal exposure to methyl salicylate on kidney function in rats were studied. Pregnant female Sprague Dawley rats were treated with methyl salicylate by intraperitoneal injections between gestational days 10 and 14. Functional assessments of renal toxicity included baseline urinary parameters, urine concentrating ability and in-vitro determination of the transport function of the renal cortex. Methyl salicylate exposure was teratogenic and embryotoxic.
Prenatal exposure decreased fetal weight and increased the number of resorptions, fetal mortality, and the incidence of fetal malformations including ectopic kidneys. The primary postnatal renal defect associated with prenatal methyl salicylate treatment was a decreased urine concentrating ability in weanlings.]
[Daston GP et al; Fundam and Appl Toxicol 11 (3): 381-400 (1988)]PEER REVIEWED****

Methyl salicylate was administered topically to pregnant hamsters at 7 day 9 hr and the teratogenic results were compared with those obtained following oral treatment with the same compound. Both treatments produced the same defect in embryos recovered at day 9: failure of fusion of the neural tube, especially in the area of the developing brain. Analysis of serum salicylate levels following both treatments produced similar curves and indicated that teratogenic levels of salicylate can reach the maternal circulation after topical exposure.
[Overman DO, White JA; Teratology 28 (3): 421-6 (1983)]PEER REVIEWED****
Three bacterial assay studies showed no mutagenic activity for Methyl Salicylate unless administered in very high doses were (>5,000 µg/plate) (MRID44213012 and 13). This limited information (carcinogenicity data from one species and genotoxicity studies from microorganisms) suggests no carcinogenic potential for Methyl Salicylate.

Dermal absorption

According to the findings in a single dose developmental toxicity study with hamsters, plasma salicylate levels reached a peak of 125 mg/100ml at 2 hours after oral

treatment with 1750 mg/kg and returned to control levels during the next 8-10 hours. Peak plasma concentrations of 50/mg/100ml were observed 5-6 hours following dermal application of 1750 mg of methyl salicylate/kg, and these plasma levels were similar to oral control values, several hours following dermal treatment. In a study increasing the dermal dose to approximately 8750 mg/kg, results in a peak plasma salicylate level of 120 mg/100ml (similar to that following oral treatment).

However, the higher dose was difficult to apply and too stressful for the animals to continue being treated, and moreover, it is a dose that is well in excess of the limit dose for an acute dermal toxicity study (>5,000 mg/kg).

There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have significantly reduced weights at birth. In addition, there is an increase in perinatal mortality, anemia, antepartum and postpartum hemorrhage, prolonged gestation, and complicated deliveries /Salicylates/ **[Gilman, A.G., T.W. Rall, A.S. Nies and P. Taylor (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY. Pergamon Press, 1990. 649]**PEER REVIEWED****

The average lethal dose /SRP: 95-98% **methyl salicylate/** for children is 10 ml, and for adults, 30 ml or 0.5 g/kg. **[Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982. 2309]**PEER REVIEWED****

6 Pharmaceutical Particulars :

6.1 List of excipients: Disodium Edetate, Carbomer 940, Propylene Glycol, Sodium Hydroxide, Acetone, Polysorbate 80, Povidone and Purified Water.

6.2 Incompatibilities: None reported.

6.3 Shelf life: 24 months

6.4 Special precautions for storage:

Do not store above 30°C. Do not freeze. Keep the tube tightly closed after use. Keep out of reach of children.

6.5 Nature and contents of container:

Lami Tubes of 20 g, 30 g, 50 g & 100 g packed in carton with package insert.

6.6 Special precaution for disposal: No special requirement.

7. REGISTRANT

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8. MANUFACTURER

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9. Date of revision of the text: May 2021