1.7 PRODUCT INFORMATION

1.7.1 SUMMARY OF PRODUCT CHARACTERISTICS

THIOZONE C
THIOCOLCHICOSIDE AND CELECOXIB CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

THIOZONE C

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Thiocolchicoside	: 8 mg
Celecoxib	: 200 mg
Excipients	: Q.S.

Approved colours used in empty capsule shell.

3. PHARMACEUTICAL FORM

Capsule
For oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Thicolchicoside is indicated for the symptomatic treatment of:
Adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards.

Celecoxib is indicated in adults for the symptomatic relief in the treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

4.2 Posology and method of administration

Thiocolchicoside:
The recommended and maximal dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days.
Paediatric population
Should not be used in children and adolescents under 16 years of age because of safety concerns
Celecoxib:
Osteoarthritis

The usual recommended daily dose is 200 mg taken once daily or in two divided doses. In some patients, with insufficient relief from symptoms, an increased dose of 200 mg twice daily may increase efficacy.

Rheumatoid arthritis

The initial recommended daily dose is 200 mg taken in two divided doses. The dose may, if needed, later be increased to 200 mg twice daily.

Ankylosing spondylitis

The recommended daily dose is 200 mg taken once daily or in two divided doses. In a few patients, with insufficient relief from symptoms, an increased dose of 400 mg once daily or in two divided doses may increase efficacy

The maximum recommended daily dose is 400 mg for all indications.

Method of administration: Oral

4.3 Contraindications

Thiocolchicoside must not be used

- in patients hypersensitive to the active substance or to any of the excipients.
- in patients with flaccid paralysis, hypotone muscle.
- during the entire pregnancy period and lactation.

Celecoxib must not be used

Hypersensitivity to the active substance or to any of the excipients.
Known hypersensitivity to sulphonamides.
Active peptic ulceration or gastrointestinal (GI) bleeding.
Breast feeding.
Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score >10).
Patients with estimated creatinine clearance <30 ml/min.
Inflammatory bowel disease.
Congestive heart failure (NYHA II-IV).

4.4 Special warnings and precautions for use

Thiocolchicoside

The dose must be reduced in case of presence of diarrhoea following oral administration.
After administration by intramuscular route episodes were observed of vasovagal syncope, thus the patient has to be monitored after being injected.
The serious cases (for example fulminant hepatitis) were observed in patients that had taken FANS or paracetamol at the same time. The patients have to be informed to report any sign of hepatic toxicity
Thiocolchicoside may precipitate seizures especially in epileptic patients or those at risk of convulsions.

Celecoxib

Gastrointestinal (GI) effects

There is further increase in the risk of gastrointestinal adverse effects for celecoxib (gastrointestinal ulceration or other gastrointestinal complications), when celecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

Concomitant NSAID use
The concomitant use of celecoxib and a non- aspirin NSAID should be avoided.
Cardiovascular effects
As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. NSAIDs, including COX-2 selective inhibitors, have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term.

4.5 Interaction with other medicinal products and other forms of interaction

Thiocolchicoside
No studies on interactions were carried out.

Celecoxib
Anticoagulants
Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of celecoxib in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications.
Anti-hypertensives
NSAIDs may reduce the effect of anti-hypertensive medicinal products including ACE-inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers.

Ciclosporin and Tacrolimus
Co-administration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when celecoxib and any of these medicinal products are combined.
Acetylsalicylic acid
Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid.

4.6 Pregnancy and lactation

Thiocolchicoside
Pregnancy
There are limited data on the use of thiocolchicoside in pregnant women. Therefore, the potential hazards for the embryo and foetus are unknown.
Studies in animals have shown teratogenic effects.

Breastfeeding
Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated during breastfeeding.

Celecoxib
Pregnancy
Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations. Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an

increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. The potential for human risk in pregnancy is unknown.

Breast-feeding
Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Administration of celecoxib to a limited number of lactating women has shown a very low transfer of celecoxib into breast milk. Women who take celecoxib should not breastfeed.

4.7 Undesirable effects

Thiocolchicoside
Disturbances in immunity system, pruritis, urticarial, hypotension, angiodoema and anaphylactic shock after intramuscular administration.
Pathology of the nervous system
drowsiness , agitation and clouding
malaise associated or to a lesser extent vasovagal syncope in the minutes following intramuscular administration, convulsions.

Celecoxib
The most commonly reported side effects when taking Celecoxib are gastrointestinal and include: upset stomach or stomach pain, diarrhoea, indigestion, bloating wind. Other side effects include: dizziness; sinusitis and upper respiratory tract infection; blurred vision; skin rash and itching; swollen hands, ankles and feet.

4.8 Overdose

Thiocolchicoside
Overdosage was not noted or reported
In case of overdosage it is recommended to get medical attention and implement symptomatic measures.

Celecoxib
There is no clinical experience of overdose. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered to healthy subjects for nine days without clinically significant adverse effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Thiocolchicoside
Pharmacotherapeutic category: Other muscle relaxant with central action
ATC code: M03BX05
Thiocolchicoside is a semisynthetic sulphide derivative of colchicoside, showing muscle relaxant pharmacological activity.
In vitro thiocolchicoside binds solely with gaba receptors and glycinergic stricnine sensitive. From the moment that thiocolchicoside acts as an antagonist of the gaba receptors, its muscle relaxant effect may be exercised to a supraspinal level, through a regulatory mechanism even though the glycinergic mechanism of action cannot be excluded.

Celecoxib
Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic drugs,
ATC CODE: M01AH01.
Celecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily). No statistically significant inhibition of COX-1 (assessed as ex vivo inhibition of thromboxane B2 [TxB2] formation) was observed in this dose range in healthy volunteers.

5.2 Pharmacokinetic properties

Thiocolchicoside
Absorption
- After oral administration, no thiocolchicoside is detected in plasma. Only two metabolites are observed:
The pharmacologically active metabolite SL18.0740 and an inactive metabolite SL59.0955. For both metabolites, maximum plasma concentrations occur 1hour after thiocolchicoside administration.
Distribution
The apparent volume of distribution of thiocolchicoside is estimated around 42.7 L after an IM administration of 8 mg. No data are available for both metabolites.
Biotransformation
After oral administration, thiocolchicoside is first metabolized in the aglycon 3-demethyltiocolchicine or SL59.0955. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged thiocolchicoside by this route of administration.
SL59.0955 is then glucuroconjugated into SL18.0740 which has equipotent pharmacological activity to thiocolchicoside and thus supports the pharmacological activity after oral administration of thiocolchicoside.
Elimination
- After oral administration, total radioactivity is mainly excreted in feces (79%) while urinary excretion represents only 20%. No unchanged thiocolchicoside is excreted either in urine or feces.

Celecoxib
Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption by about 1 hour.
Celecoxib is mainly eliminated by metabolism. Less than 1% of the dose is excreted unchanged in urine. The inter-subject variability in the exposure of Celecoxib is about 10-fold. Celecoxib exhibits dose- and time-independent pharmacokinetics in the therapeutic dose range. Plasma protein binding is about 97% at therapeutic plasma concentrations and the drug is not preferentially bound to erythrocytes. Elimination half-life is 8-12 hours.
Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been identified in human plasma i.e., a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose	BP
Croscarmellose Sodium	BP

Sodium Lauryl Sulphate	
Colloidal Anhydrous Silica	BP
Povidone	BP
Isopropyl Alcohol	BP
Magnesium Stearate	BP
Purified Talc	BP
Green/Blue Size '0'	IHS

6.2 Incompatibilities
NA

6.3 Shelf life
24 Months

6.4 Special precautions for storage

Store below 30°C.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container
1 X 10 Alu-Alu Blister Pack

6.6 Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER

Saga LABORATORIES
Ahmedabad
Gujarat, India.
E-mail: info@sagalabs.com
URL: www.sagalabs.com

8. MARKETING AUTHORISATION NUMBER(S)

G/25/1877