Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Pynact plus

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:
Paracetamol 325mg
Celecoxib 200mg

3. Pharmaceutical form

Hard gelatin capsule

A Orange / white coloured, Size "0" hard gelatin capsules containing a white coloured powder.

4. Clinical particulars

4.1 Therapeutic indications

Pynact plus is indicated in adults for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2 Posology and method of administration

Oral: The lowest effective daily dose should be used to avoid cardiovascular risks. The patient's need for symptomatic relief and response to therapy should be reevaluated periodically, especially in patients with osteoarthritis.
Osteroarthritis: The usual recommended daily dose is one capsule
Rheumatoid arthritis: The initial recommended daily dose is one capsule.
Ankylosing spondylitis: The recommended daily dose is one capsule
The maximum recommended daily dose for all indications is two capsules.
Method of administration
Capsules is for oral administration. The capsules may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Known hypersensitivity to sulphonamides. Active peptic ulceration or gastrointestinal bleeding. Patients who have experienced asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic type reactions after taking acetylsalicylic acid (aspiring) or other NSAIDs including COX-2(cyclooxygenase-2) inhibitors. Pregnant and lactating women should take care while having this drug unless using an effective method of contraception. Celecoxib has shown to cause

malformation in the two animal species and hence the potential for human risk in pregnancy is unknown but cannot be excluded. Severe hepatic dysfunction (serum albumin < 30 ml/min. Inflammatory bowel disease. Congestive heart failure. Established ischaemic heart disease, peripheral arterial disease and / or cerebrovascular disease. Contraindications to using acetaminophen include hypersensitivity to acetaminophen, severe hepatic impairment or severe hepatic active disease. However, hepatic impairment is truly a limiting factor, as it would likely be associated with decreased production of the toxic metabolite, N-acetyl-pbenzoquinoneimine.

4.4 Special warnings and precautions for use

Paracetamol should be given with care in patients with impaired kidney or liver function, in alcoholism and in patients taking drugs that affect the liver. Its absorption may be accelerated by Metoclopramide. Excretion may be affected and plasma concentrations altered when administered with Probencid. Gastrointestinal effects: Upper and lower gastrointestinal complications (like perforations, ulcers or bleedings), some of them resulting in fatal outcome have occurred in patients treated with celecoxib. There is further increase in the risk associated with gastrointestinal adverse effects of celecoxib (gastrointestinal ulceration or other gastrointestinal complications), when celecoxib is taken concomitantly with acetylsalicylic acid (even at low doses). Concomitant NSAID use: Use of celecoxib and non-aspirin NSAID should be avoided. Cardiovascular effects: NSAIDs including COX-2 selective inhibitors, are associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. Patients with risk factors of cardiovascular events (like hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with celecoxib after careful analysis. Fluid retention and oedema: Cases of fluid retention and oedema is observed in pateints taking celecoxib. As a result, celecoxib should be used in patients with history of cardiac failure, left ventricular dysfunction or hypertension and also in patients with pre-existing oedema due to other reasons as prostaglandin inhibition may result in deterioration of renal function and fluid retention; also, in patients with diuretic treatment, caution is advised. Hypertension: There are chances of onset of new hypertension or worsening of preexisting hypertension, either of which will contribute to the increased risk of cardiovascular events. Hepatic and renal effects: There are chances of renal toxicity. Patients at greatest risk of renal toxicity are those who have impaired renal function, heart failure, liver dysfunction, those on diuretics, angiotensin converting enzyme (ACE)-inhibitors, angiotensin II receptor antagonists and the elderly. Cases of hepatic toxicity include fulminant hepatitis, liver necrosis and hepatic failure. The onset of adverse effects starts within one month after initiation of celecoxib treatment. CYP2D6 inhibition: Celecoxib inhibits CYP2D6. Reduction in the dose is necessary for individually dose-titrated medicinal products that are metabolized by CYP2D6.

Skin and systemic hypersensitivity reactions: Serious skin reactions like exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been observed by the use of celecoxib. Patients who have a sulfonamide allergy or a drug allergy are at a serious risk of skin reactions. Use with other anticoagulants: On concurrent therapy with warfarin, bleeding events have been reported. Increased prothrombin time has been reported. There should be close monitoring of patients on treatment with warfarin/coumarin type oral anticoagulants.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol (acetaminophen) is one of the most commonly used analgesic antipyretic drugs worldwide, and it is widely available by prescription and over the counter (OTC). Fortunately, few clinically significant drug interactions have been documented. There is probable potentiation of hepatotoxicity following an overdose from the paracetamol metabolite NAPQI by enzyme-inducing drugs. There is considerable controversy regarding the possible interaction with warfarin in its potential to increase its anticoagulant effects because of discrepancies between observational studies and those in healthy volunteers. Otherwise, no serious adverse drug interactions with therapeutic doses of paracetamol have been confirmed in humans. Because the absorption of paracetamol is so dependent on gastric emptying, other drugs that alter gastric emptying can change its pharmacokinetics; but this would not cause serious adverse effects. Although animal experiments have demonstrated that many compounds can modify paracetamol hepatotoxicity, these are unlikely to be important at therapeutic doses. Paracetamol may affect the results of laboratory tests for uric acid and blood sugar levels. Celecoxib: Anticoagulant therapy should be monitored as there is a increased risk of bleeding complications. Antihypertensive effect of medicinal products including ACE inhibitors, angiotensin II receptor antagonists, diuretics and beta blockers is seen. The risk acute renal insufficiency, which is reversible may be increased in patients with compromised renal function (e.g. dehydrated patients, patients on diuretics or elderly patients) when ACE inhibitors, angiotensin II receptor antagonists and / or diuretics are combined with NSAIDs, including celecoxib. Ciclosporin and Tacrolimus: Concomitant use of celecoxib with these drugs increases the nephrotoxic effect of ciclosporin and tacrolimus. Renal function has to be monitored when combined with celecoxib. Acetylsalicylic acid: There is an increased risk of gastro-intestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone was shown for concomitant administration of low dose acetylsalicylic acid. CYP2D6 inhibition: Celecoxib is an inhibitor of CYP2D6. There will be an increase in the plasma concentration of products which are substrates of this enzyme. Oral contraceptives: Studies have shown that celecoxib has no clinically relevant effects on the pharmacokinetics of oral contraceptives.

4.6 Fertility, pregnancy, and lactation

Pregnancy:
The drug is contraindicated in pregnancy and who become pregnant women. The drug is to be discontinued in individuals who become pregnant during treatment. During second or third trimester of pregnancy, NSAIDs including celecoxib may cause fetal renal dysfunction resulting in reduction of amniotic fluid volume or oligohydramnios. These effects are not reversible.
Breast-feeding:
The drug is not recommended in breast-feeding women as celecoxib is into breast milk in low amounts.
Fertility:
There is delay or prevent rupture of ovarian follicles which is associated with reversible infertility in some women.
Paediatric use
Celecoxib is not intended for use in children.

4.7 Effects on ability to drive and use machines.
Not applicable

4.8 Undesirable effects
Allergic reactions, which may be severe and include:

- Skin rashes, itching or hives
- Swelling of the throat, tongue or face
- Shortness of breath or wheezing
- Skin rash or peeling, or mouth ulcers
- Breathing problems. This is more likely if you have experienced them before when taking other painkillers such as ibuprofen and aspirin
- Unexplained bruising or bleeding or becoming unusually tired. Getting more infections than usual.
- Liver problems. Nausea, sudden weight loss, loss of appetite and yellowing ofthe eyes and skin can occur
- Like all NSAIDs, celecoxib carries an FDA boxed warning for cardiovascular
- risk, including the increased risk of heart attacks and strokes. As a selective COX-2 inhibitor, celecoxib also faces scrutiny for increased cardiovascular risk since another selective COX-2 inhibitor, rofecoxib, was withdrawn from production in 2004 due to cardiovascular risk concerns. Extensive reviews have had mixed results regarding whether celecoxib carries non-inferior or increased cardiovascular risk compared to ibuprofen and naproxen.
- Also, like all NSAIDs, celecoxib carries an additional FDA boxed warning for gastrointestinal (GI) effects, including bleeding, ulceration, and perforation of the stomach and intestines. This adverse effect makes it particularly dangerous to susceptible populations such as the elderly.
- In addition to these, celecoxib may cause new or worsening hypertension, fluid retention in patients with congestive heart failure, renal toxicity, liver toxicity, anaphylactic reactions, and skin

changes ranging from a non-severe rash to Stevens-Johnson syndrome.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

If you miss a dose, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to regular schedule. Do not double the dose. Overdose of paracetamol may occur after an acute single ingestion of a large amount of paracetamol or paracetamol containing medication or repeated ingestion of an amount exceeding recommended dosage. Patients are often asymptomatic or have only mild gastrointestinal symptoms at initial presentation. Untreated paracetamol poisoning may cause varying degrees of liver injury over the 2 to 4 days following ingestion, including fulminant hepatic failure. Rarely massive overdose may initially present with coma and severe metabolic acidosis. Hepatotoxicity is extremely rare in patients treated with acetylcysteine within 8 hours of an acute paracetamol overdose. There is no clinical experience of overdose. In the event of any suspected overdose, supportive clinical treatment is to be given.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Paracetamol:

- Pharmacotherapeutic group: Analgesic and antipyretic,
- ATC Code: N02B E01

Celecoxib:

- Pharmacotherapeutic Group : Non-steroidal anti-inflammatory and antirheumatic drug, Selective COX 2 inhibitors
- ATC Code : M01AH01

Acetaminophen's exact mechanism of action has not been fully established, according to the FDA label, it is categorized as an NSAID (a nonsteroidal antiinflammatory drug) due to that fact that it inhibits the cyclooxygenase (COX) pathways, and it is thought to exert central actions which ultimately lead to the alleviation of pain symptoms. One theory is that acetaminophen increases the pain threshold by inhibiting two isoforms of cyclooxygenase, COX-1 and COX-2, which are involved in prostaglandin (PG) synthesis. Prostaglandins are responsible for eliciting pain sensations. Acetaminophen does not inhibit cyclooxygenase in peripheral tissues and, therefore, has no peripheral anti-inflammatory effects. Though acetylsalicylic acid (aspirin) is an irreversible inhibitor of COX and directly blocks the active site of this enzyme, studies have shown that acetaminophen (paracetamol) blocks

COX indirectly. Studies also suggest that acetaminophen selectively blocks a variant type of the COX enzyme that is unique from the known variants COX-1 and COX-2. This enzyme has been referred to as COX-3. The antipyretic actions of acetaminophen are likely attributed to direct action on heat-regulating centers in the brain, resulting in peripheral vasodilation, sweating, and loss of body heat. The exact mechanism of action of this drug is not fully understood at this time, but future research may contribute to deeper knowledge. Celecoxib is chemically designated as 4-[5-(4-methylphenyl)- 3-(trifluoromethyl)-1Hpyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The mechanism of action of celecoxib is due to selective inhibition of cyclooxygenase-2 (COX-2), which is responsible for prostaglandin synthesis, an integral part of the pain and inflammation pathway. This pharmacologic activity gives celecoxib its analgesic, antiinflammatory, and antipyretic effects. Celecoxib weakly inhibits COX-1 and, therefore, may affect platelet function less than aspirin. Celecoxib also has anticancer properties discussed below and exerts its anticancer properties by binding cadherin-11 (CDH11), which likely plays a significant role in the malignant progression of cancerous cells. Celecoxib is extensively metabolized through cytochrome P450 2C9 (CYP2C9) and may have interactions with other medications that are substrates of CYP2C9.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, paracetamol it is rapidly absorbed from the gastrointestinal tract, its systemic bioavailability being dose-dependent and ranging from 70 to 90%. Celecoxib is absorbed rapidly from the gastrointestinal tract.

Distribution:

After absorption, paracetamol volume of distribution is roughly 50 L. The concentration in serum after a typical dose of paracetamol usually peaks below 30 µg/ml (200 µmol/L). After 4 hours, the concentration is usually less than 10 µg/ml (66 µmol/L). The apparent volume of distribution of celecoxib at steady state (Vss/F) is about 429 L, which suggests wide distribution into various tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism & Excretion:

Paracetamol is metabolized primarily in the liver, into toxic and nontoxic products. The mean plasma elimination half-life is around 4 hours. A large part of celecoxib metabolism is mediated by cytochrome P450 2C9 in the liver with some contribution from CYP3A4 and CYP2C8 and possible contributions from CYP2D6. It is metabolized by biotransformation to carboxylic acid and glucuronide metabolites. Three metabolites, a primary alcohol, a carboxylic acid, and a glucuronide conjugate, have been found in human plasma after celecoxib administration. These are considered inactive metabolites in regards to COX enzyme inhibition. Patients who are known or suspected to have decreased cytochrome P450 2C9 activity or function,

based on their previous history, should be administered celecoxib with caution as they may have abnormally high serum concentrations resulting from decreased metabolism celecoxib. Celecoxib is primarily eliminated by hepatic metabolism with small amounts (<3%) of the unchanged drug found in both the urine and feces. About 57% of an oral dose of celecoxib is excreted in the feces and 27% is found to be excreted into the urine in the form of metabolites. The main metabolite in urine and feces is identified as the carboxylic acid metabolite (73%). The amount of glucuronide in the urine is reported to be low.

5.3 Preclinical safety data

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that aciclovir does not pose a genetic risk to man.

Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse.

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of orally administered aciclovir on fertility.

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice.

In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

6. Pharmaceutical particulars

6.1 List of excipients

Ethyl cellulose
Sodium benzoate,
Isopropyl alcohol
Orange/white coloured hard gelatin capsule size “0”.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage:

Store at a temperature below 25°C protected from heat and light.

6.5 Nature and contents of container

Alu-alu blister pack Pack Size: 10 x 1 x 10

6.6 Special precautions for disposal and other handling:

No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
CURIS LIFESCIENCES PVT. LTD.
Manufacturing site address:
Curis Lifesciences Pvt. Ltd.
PF-23, G.I.D.C. II, Sanand,
Ahmedabad-382 110, Gujarat-India
info@curisls.com

8. Marketing authorization number

H2024/CTD10727/23020

9. Date of first registration

16/02/2024

10. Date of revision of the text:

November 2024