SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Combodex IV

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL vial contains paracetamol 1000 mg and ibuprofen (as sodium dihydrate) 300 mg.

Excipient with known effect:
Sodium 35.06 mg per 100 ml (0.35 mg/ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Combodex IV is indicated in adults for the relief of mild to moderate pain and the reduction of fever, where an intravenous route of administration is considered clinically necessary.

4.2 Posology and method of administration

Posology
Administer one vial (100 mL) Combodex IV as a 15-minute infusion every 6 hours, as necessary. Do not exceed a total daily dose of 4000 mg (4 g) paracetamol.

Special populations

Paediatric population

The safety and efficacy of Combodex IV in children aged under 18 years have not been established.

Elderly

Clinical studies of Combodex IV did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently to younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients are at increased risk for serious GI adverse events (see section 4.4, Gastrointestinal events).

Renal impairment

Caution is also recommended in patients with pre-existing renal disease. No information is available from controlled clinical studies regarding the use of Combodex IV in patients with advanced renal disease. If Combodex IV therapy must be initiated in patients with advanced renal disease, closely monitor the patient's renal function.

Hepatic impairment

The use of paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepaticfailure and death.

A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ibuprofen. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), Combodex IV should be discontinued.

Adverse gastrointestinal events
To minimise the potential risk for an adverse GI event in patients treated with a NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected.

This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Method of administration
Combodex IV should be administered as a 15-minute intravenous infusion.

Visually inspect Combodex IV for particulate matter and discolouration prior to administration, whenever solution and container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.

Combodex IV should be used in one patient on one occasion only. It contains no antimicrobial preservative. Unused solution should be discarded.

As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the perfusion applies particularly for central route infusion, in order to avoid air embolism.
It is recommended that for the administration of Combodex IV a syringe or giving set with a diameter equal to or below 0.8 mm should be used for solution sampling. In addition, it is recommended that the bung is pierced at the location specifically designed for needle introduction (where the thickness of the bung is the lowest). If these recommendations are not adhered to the likelihood of bung fragmentation or the bung being forced into the vial is increased.

To facilitate administration, the label attached to the vials of Combodex IV allows hanging.

4.3 Contraindications

This product is contraindicated for use:
- in patients with known hypersensitivity to paracetamol, ibuprofen, other NSAIDs or to any ofthe excipients listed in section 6.1;
- in patients with severe heart failure (NYHA Class IV);
- in patients with active alcoholism, as chronic excessive alcohol ingestion may predispose patients to hepatotoxicity (due to the paracetamol component);

- in patients who have experienced asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid or other NSAIDs;
- in patients with a history of gastrointestinal bleeding or perforation related to previous NSAIDtherapy;
- in patient with active, or a history of, recurrent peptic ulceration/haemorrhage (two or moredistinct episodes of proven ulceration or bleeding);
- in patients with severe hepatic failure or severe renal failure (see section 4.4.);
- in patients with cerebrovascular or other active bleeding;
- in patients with blood clotting disorders and conditions involving an increased tendency tobleed;
- in patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake);
- during the third trimester of pregnancy (see section 4.6);

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. Use of the recommended maximum dose of Combodex IV of 100 mL every 6 hours has only been studied for a period of up to 2 days.

The use of Combodex IV with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided.

Do not give anything else containing paracetamol while giving this medicine.

In order to avoid the risk of overdose,
- check that other medicinal products do not contain paracetamol or ibuprofen,
- observe the maximum recommended doses (see section 4.2).

Cardiovascular thrombotic events
Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarctionor stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. 1200 mg/day)is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemicheart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Hepatic impairment
The use of paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepaticfailure and death. Also, patients with impaired liver function or a history of liver disease, and who are on long term ibuprofen therapy or paracetamol treatment, should have hepatic function monitored at regular intervals, as ibuprofen has been reported to have a minor and transient effect on liver enzymes.Dose reduction is recommended in patients showing signs of worsening hepatic function. Treatment should be stopped in those patients who develop severe liver failure (see section 4.3).

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reportedwith ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia,rash, etc.), ibuprofen should be discontinued. Both active drugs have been reported to cause hepatotoxicity and even hepatic failure, especially paracetamol.

Renal impairment
Paracetamol can be used in patients with chronic renal disease without dosage adjustment. There is minimal risk of paracetamol toxicity in patients with moderate to severe renal failure. However, for theibuprofen component of this product, caution should be used when initiating treatment with ibuprofen in patients with dehydration. The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown.NSAIDs have been reported to cause nephrotoxicity in various forms: interstitial nephritis, nephritic syndrome and renal failure. Renal impairment from ibuprofen use is usually reversible. In patients withrenal, cardiac or hepatic impairment, those taking diuretics and ACE inhibitors, and the elderly, cautionis required since the use of NSAIDs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored in these patients. Treatment should be stopped in those patients who develop severe renal failure (see section 4.3).

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs, diuretics and thiazide diuretics
The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from thesethree classes should be used with caution particularly in elderly patients or those with pre-existing renalimpairment.

Elderly
No reduction in recommended dosage is necessary. However, caution should be taken with regard to the use of ibuprofen as it should not be taken by adults over the age of 65 without consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastrointestinal ulceration and renal impairment.

Haematological effects
Blood dyscrasias have been rarely reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

Anaphylactoid reactions
As standard practice during intravenous infusion, close patient monitoring is recommended, especiallyat the beginning of the infusion to detect any anaphylactic reaction caused by the active substance or the excipients.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very rarely observed. At the first signs of a hypersensitivity reaction following the administration of Combodex IV, therapy

must be stopped and symptomatic treatment must be established. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Coagulation defects
Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effectmay be exaggerated in patients with underlying haemostatic defects, products containing ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulationtherapy. Patients with coagulation disorders or those undergoing surgery should be monitored. Specialmedical vigilance is required for use in patients immediately after undergoing major surgery.

Gastrointestinal events
Gastrointestinal (GI) bleeding, ulceration or perforation, which can be fatal, have been reported with allNSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid,or other medicinal products likely to increase gastrointestinal risk (see below and section 4.5). Patientswith a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms(especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the riskof ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

Due to the ibuprofen component, Combodex IV should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn’s disease) as well as in patients with porphyria.

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

This product should be discontinued if there is any evidence of gastrointestinal bleeding or ulceration.

Hypertension
NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patientstaking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure
Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore

caution is advised in patients with fluid retention or heart failure.

Severe skin reactions
NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur withoutwarning. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Patients appear to be at highest risk for these reactions early in the courseof therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment.

Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Exceptionally, varicella can cause serious cutaneous and soft tissues infectious complications. To date,the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Combodex IV in case of varicella.

Pre-existing asthma
Products containing ibuprofen should not be administered to patients with acetylsalicylic acid-sensitiveasthma and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects
Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who developvisual disturbances during treatment with products containing ibuprofen should have an ophthalmological examination.

Aseptic meningitis
For products containing ibuprofen, aseptic meningitis has been reported only rarely, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Potential laboratory test interferences
Using current analytical systems, paracetamol does not cause interference with laboratory assays. However, there are certain methods with which the possibility of laboratory interference exists, as described below:

Urine tests
Paracetamol in therapeutic doses may interfere with the determination of 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding paracetamol ingestion several hours before and during the collection of the urine specimen.

Masking of symptoms of underlying infections
Combodex IV can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment andthereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Combodex IV is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Prolonged use of analgesics
On prolonged use of analgesics, headache may occur which must not be treated by increasing the

doseof the medicinal product.

Flucloxacillin
Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported, in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism), who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Special precautions
There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on stopping the medicine.

Ibuprofen should be used only after strict assessment of the benefit/risk in patients with congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularlythose that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Caution is required in patients with certain conditions, which may be made worse:
- In patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of this medicinal product.
- In patients who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reaction occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.

This medicinal product contains 35.06 mg sodium per 100 ml vial, equivalent to 1.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

This medicinal product should not be taken with other medicinal products containing paracetamol, ibuprofen, acetylsalicylic acid, salicylates or with any other anti-inflammatory drugs (NSAIDs) unlessunder a doctor's instruction.

<u>Ibuprofen:</u>
As with other ibuprofen-containing products, the following combinations with Combodex IV should be avoided:
- *The dicumarol group:* NSAIDs may increase the effect of anticoagulants such as warfarin. Experimental studies show that ibuprofen reinforces the effects of warfarin on bleeding time. NSAIDs and the dicumarol group are metabolised by the same enzyme, CYP2C9.
- *Antiplatelet agents:* NSAIDs should not be combined with antiplatelet agents such as ticlopidinedue to the additive inhibition of the platelet function (see below).
- *Methotrexate:* NSAIDs inhibit the tubular secretion of methotrexate and some metabolic interaction with reduced clearance of methotrexate may also occur as a result. The risk of a potential interaction between an NSAID and methotrexate should also be taken into account in connection with low-dose treatment with methotrexate, especially in patients with renal impairment. Whenever combination treatment is given, renal function should be

monitored.

Caution should be exercised if both an NSAID and methotrexate are given within 24 hours, as the plasma levels of methotrexate can increase, resulting in increased toxicity. Accordingly, in high-dose treatment with methotrexate one should always avoid prescribing NSAIDs.

- *Acetylsalicylic acid:* Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Experimental datasuggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long- term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).
- *Lithium*: Ibuprofen reduces the renal clearance of lithium, as a result of which serum lithium levels may rise. The combination should be avoided unless frequent checks of serum lithiumcan be carried out and a possible reduction in the dose of lithium made.
- *Cardiac glycosides:* NSAIDs can exacerbate heart failure, reduce glomerular filtration and increase plasma cardiac glycoside (e.g. digoxin) levels.
- *Mifepristone:* A decrease of the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy
- *ACE inhibitors and angiotensin-II antagonists:* There is an increased risk of acute renal failure, usually reversible, in patients with renal impairment (e.g. dehydrated and/or elderly patients) when treatment with ACE inhibitors or angiotensin-II antagonists is given at the same time as NSAIDs, including selective cyclooxygenase-2 inhibitors. The combination should, therefore, be given with care to patients with renal impairment, especially elderly patients. Patients shouldbe adequately hydrated and a check of renal function should be considered after the initiation ofcombination treatment and at regular intervals during treatment (see section 4.4).
- *Beta-blockers*: NSAIDs counteract the antihypertensive effect of beta-adrenoceptor blocking drugs.
- *Sulphonylureas:* There are rare reports of hypoglycaemia in patients on sulphonylurea medications receiving ibuprofen.
- *Zidovudine:* There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- *Quinolone antibiotics:* animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have increased risk of developing convulsions.
- *Thiazides, thiazide-related preparations and loop diuretics*: NSAIDs can counteract the diureticeffect of furosemide and bumetanide, possibly through inhibition of prostaglandin synthesis. They can also counteract the antihypertensive effect of thiazides.
- *Potassium sparing diuretics*: The concomitant use may lead to hyperkalaemia.
- *Aminoglycosides*: NSAIDs may reduce the excretion of aminoglycosides.
- *Selective serotonin re-uptake inhibitors (SSRIs):* SSRIs and NSAIDs each entail an increased risk of bleeding, e.g. from the gastrointestinal tract. This risk is increased by combination therapy. The mechanism may possibly be linked to reduced uptake of serotonin in the platelets (see section 4.4).
- *Cyclosporine:* The concomitant administration of NSAIDs and cyclosporine is thought to be

capable of increasing the risk of nephrotoxicity due to decreased synthesis of prostacyclin in thekidney. Accordingly, in the event of combination treatment, renal function must be monitored closely.

- *Captopril*: Experimental studies indicate that ibuprofen counteracts the effect of captopril on sodium excretion.
- *Tacrolimus*: Concomitant administration of NSAIDs and tacrolimus is thought to be capable of increasing the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. Accordingly, in the event of combination treatment, renal function should be monitored closely.
- *Corticosteroids:* Concomitant treatment gives rise to an increased risk of gastrointestinal ulceration or bleeding.
- *CYP2C9 Inhibitors:* Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors) an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.
- *Phenytoin*: Plasmatic levels of phenytoin may be increased in the concomitant treatment with ibuprofen and therefore the risk of toxicity may increase.
- *Probenecid and sulfinpyrazone*: Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.
- *Herbal extracts*: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

Paracetamol:

- Probenecid inhibits the binding of paracetamol to glucuronic acid, thus leading to a reduction in paracetamol clearance by a factor of approximately 2. In patients concurrently taking probenecid,the paracetamol dose should be reduced.
- Enzyme-inducing drugs such as certain antiepileptics (phenytoin, phenobarbital, carbamazepine)decreased plasma AUC of paracetamol to approximately 60% in pharmacokinetic studies. Other substances with enzyme-inducing properties (i.e. rifampicin, *Hypericum*) could also result in decreased concentrations of paracetamol. In addition, the risk of liver damage during treatment with the maximum recommended dose of paracetamol is probably higher in patients who receiveenzyme-inducing drugs.
- Zidovudine may affect paracetamol metabolism and vice versa, which may add to the toxicityof both.
- Anticoagulant drugs (warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid alone or with other drugs for tuberculosis
- Paracetamol may affect the pharmacokinetics of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining paracetamol with chloramphenicol injection treatment.
- Ethyl alcohol potentiates paracetamol toxicity, possibly by inducing hepatic production of paracetamol-derived hepatotoxic products.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)

Effects on laboratory tests

Intake of paracetamol can affect tests for uric acid using phosphotungstic acid and blood sugar testsusing glucose-oxidase-peroxidase.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experience of use of this product in humans during pregnancy. Because of the ibuprofen-component Combodex IV is contraindicated during the third trimester of pregnancy (see below).

For ibuprofen

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiacmalformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. Theabsolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration ofa prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation lossand embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above), which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at verylow doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Combodex IV is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

For paracetamol

A large amount of data on pregnant women using paracetamol indicate neither malformative, nor

foeto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breastfeeding
Paracetamol is excreted in breast milk but not in a clinically significant amount and available published data do not contraindicate breastfeeding as long as the recommended dosage is not exceeded.

Ibuprofen and its metabolites can pass in very small amounts into breast milk. With therapeutic doses during short term treatment the risk for influence on infant seems unlikely.

In light of the above evidences it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

Fertility
The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility,withdrawal of the product should be considered.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Clinical trials with Combodex IV and paracetamol 500 mg/ibuprofen 150 mg film-coated tablets have not indicated any other undesirable effects other than those for paracetamol alone or ibuprofen alone.

The adverse reactions are listed below as MedDRA preferred term by system organ class and absolutefrequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000
to <1/1,000); very rare (<1/10,000); Frequency not known (cannot be estimated from the available data)

Infections and infestations	**Very rare:** Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described.
Blood and lymphatic system disorders	**Uncommon**: Decrease in haemoglobin and haematocrit. Although a causal relationship has not been established, bleeding episodes (e.g. epistaxis, menorrhagia) have been reported in during therapy with the drug. **Very Rare**: Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia with or without purpura) have been reported following ibuprofen use, but were not necessarily causally related to the drug.

Immune system disorders	**Very Rare**: Hypersensitivity reactions including skin rash and cross-sensitivity with sympathomimetics have been reported. **Uncommon**: Other allergic reactions have been reported but a causal relationship has not been established: Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema.
Metabolic and nutrition disorders	**Very Rare**: In the case of metabolic acidosis, causality is uncertain as more than one drug was ingested. The case of metabolic acidosis followed the ingestion of 75 grams of paracetamol, 1.95 grams of acetylsalicylic acid, and a small amount of a liquid household cleaner. The patient also had a history of seizures which the authors reported may have contributed to an increased lactate level indicative of metabolic acidosis. Metabolic sideeffects including metabolic acidosis have been reported following amassive overdose of paracetamol. **Uncommon**: Gynaecomastia, hypoglycaemic reaction. **Not Known**: Hypokalaemia[1], High anion gap metabolic acidosis[3].
Nervous system disorders	**Common**: Dizziness, headache, nervousness. **Uncommon**: Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma. **Rare**: Paraesthesia, hallucinations, dream abnormalities. **Very Rare**: Paradoxical stimulation, optic neuritis, psychomotor impairment, extrapyramidal effects, tremor and convulsions.
Eye disorders	**Uncommon:** Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) have occurred but is usually reversed after cessation of therapy. Any patient with eye complaints should have an ophthalmological examination which includes central vision fields.
Ear and labyrinth disorders	**Very Rare**: Vertigo. **Common**: Tinnitus (for medicines containing ibuprofen).
Cardiac disorders	**Common**: Oedema, fluid retention; fluid retention generally responds promptly to discontinuation of the drug. **Very Rare**: Palpitations; tachycardia; arrhythmia and other cardiac dysrhythmias have been reported. Hypertension and cardiac failure have been reported in association with NSAID treatment.[2]
Respiratory and thoracic and mediastinal disorders	**Uncommon**: Thickened respiratory tract secretions. In children undergoing tonsillectomy, stridor has been reported. Hypoxemia has been reported. **Very Rare**: Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea.
Gastrointestinal Disorders	**Common**: Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting, flatulence, constipation, slight gastrointestinal blood loss that may cause anaemia in exceptional cases. **Uncommon**: Peptic/gastrointestinal ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly. Ulcerative stomatitis and exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently gastritis has been observed and pancreatitis reported. Acid peptic disease has been reported. **Very rare:** Oesophagitis, formation of intestinal diaphragm-like strictures.

Hepatobiliary disorders	**Very Rare**: Hepatic damage, especially during long-term treatment, hepatic failure. Abnormal liver function, hepatitis and jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury.
Skin and subcutaneous tissue disorders	**Common**: Rash (including maculopapular type), pruritus. **Very Rare**: Alopecia. Hyperhidrosis, purpura and photosensitivity. Exfoliative dermatoses. Bullous reactions including erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Very rare cases of serious skin reactions have been reported. In exceptional cases, severe skin infections and soft-tissue complications may occur during varicella infection. **Not known**: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP).
Renal and urinary disorders	**Uncommon**: Urinary retention **Rare:** Kidney tissue damage (papillary necrosis), particularly in long-term therapy. **Very Rare**: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure. Adverse renal effects are most often observed after overdose, after chronic abuse (often with multiple analgesics), or in association with paracetamol-related hepatotoxicity. Acute tubular necrosis usually occurs in conjunction with liver failure,but has been observed as an isolated finding in rare cases. A possible increase in the risk of renal cell carcinoma has been associated with chronic paracetamol use as well. One case-control study of patients with end-stage renal disease suggested that long term consumption of paracetamol may significantly increase the risk of end-stage renal disease particularly in patients taking more than 1000 mg per day. **Not Known:** Renal tubular acidosis[1]
General disorders and administration site conditions	**Uncommon**: Pyrexia **Very Rare:** Fatigue and malaise.
Injury, poisoning and procedural complications	**Uncommon**: Post-operative haemorrhage following tonsillectomy has been reported.
Investigations	**Common**: Alanine aminotransferase increased, gamma-glutamyl transferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased. **Uncommon**: Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, haemoglobin decreased and platelet count increased. **Rare:** elevated uric acid concentrations in the blood.

Description of selected adverse events

1. Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.
2. Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial

infarctionor stroke) (see section 4.4).
3. High anion gap metabolic acidosis: Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose

Symptoms

Paracetamol

Liver injury and even failure can occur following paracetamol overdose. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damagemay become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism andmetabolic acidosis may occur. In severe poisoning, hepatic failure may proceed to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop in the absence of severe liver damage. Cardiac arrhythmias have been reported. Liver damage is possible in adults who have taken 10 g or more of paracetamol, due to excess quantities of a toxic metabolite.

Ibuprofen

Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.
In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur.
Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see sections 4.4 and 4.8).

Treatment

Paracetamol

Prompt treatment is essential in the management of paracetamol overdose even when there are no obvious symptoms, because of the risks of liver injury, which presents after some hours or even days delay. Medical treatment is advised, without delay in any patient who has ingested 7.5 g or more of paracetamol in the preceding 4 hours. Gastric lavage should be considered. Specific therapy to reverseliver injury with an antidote such as acetylcysteine (intravenous) or methionine (oral) should be instituted as soon as possible.
Acetylcysteine is most effective when administered during the first 8 hours following ingestion of the overdose and the effect diminishes progressively between 8 and 16 hours. It used to be believed that starting treatment more than 15 hours after overdose was of no benefit and might possibly aggravate therisk of hepatic encephalopathy. However, late administration has now been shown to be safe, and studiesof patients treated up to 36 hours after ingestion suggest that beneficial results may be obtained beyond15 hours. Furthermore, administration of intravenous acetylcysteine to patients who have already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.
An initial dose of 150 mg/kg of acetylcysteine in 200 mL 5% glucose is given intravenously

over 15 minutes, followed by an I.V. infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and then
100 mg/kg in 1 litre 5% glucose over 16 hours. The volume of I.V. fluids should be modified for children.

Methionine is given orally as 2.5 g every 4 hours up to 10 g. Methionine treatment must be started within 10 hours after ingestion of paracetamol; otherwise it will be ineffective and may exacerbate liverdamage.
Evidence of serious symptoms may not become apparent until 4 or 5 days following overdose and patients should be carefully observed for an extended period.

Ibuprofen
Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric lavage is only recommended within 60 minutesafter ingestion of a life-threatening dose. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, theuse of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen tablets.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Analgesics and Antipyretics, Anilides; ATC code:

N02BE51.

Mechanism of action

Although the exact site and mechanism of analgesic action of paracetamol is not clearly defined, it appears that it induces analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. Thedrug's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase,leading to reduction in prostaglandin synthesis.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylicacid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies showthat when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regardingextrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

Clinical trials
Clinical studies of Combodex IV did not include subjects 65 years of age and over to determine whether they respond differently to younger subjects.

In a phase III efficacy study in 276 patients with mild to moderate pain following bunionectomy surgery,
Combodex IV provided greater pain relief than placebo or comparable doses of paracetamol or

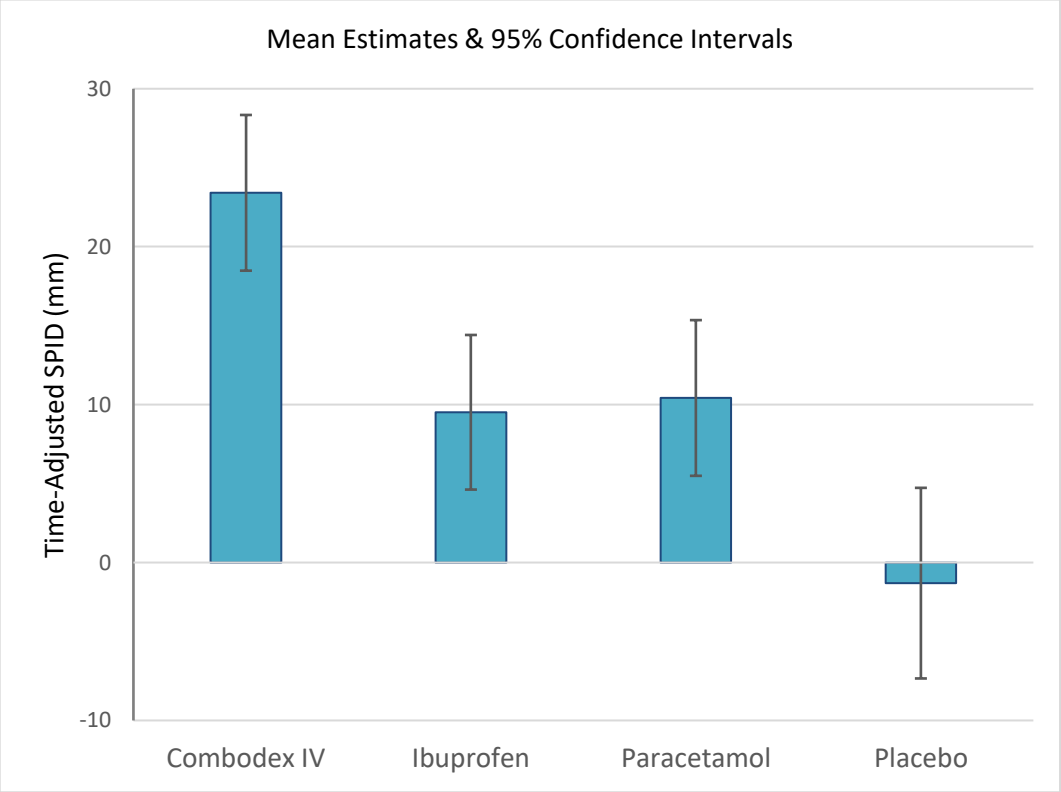
ibuprofen alone.

The analysis of time-adjusted Summed Pain Intensity Difference (SPID) 0-48 hours demonstrated that Combodex IV (mean=23.41, SE=2.50) provided more effective pain relief than placebo (mean= -1.30, SE=3.07),paracetamol (mean=10.42, SE=2.50) or ibuprofen (mean=9.51, SE=2.49), with a high level of statistical significance (p<0.001).

Table 1: Summary of Time-adjusted SPID (0-48 hours) by Treatment Group.

	Combodex IV	Ibuprofen	Paracetamol	Placebo
	N=75	N=76	N=75	N=50
Mean (SE)	23.41 (2.89)	9.51 (2.53)	10.42 (2.49)	-1.30 (2.08)
Median	23.10	5.40	3.45	-4.00
Min ; Max	-34.08 ; 74.17	-30.68 ; 79.98	-26.78 ; 65.43	-22.42 ; 47.50
Mean Estimate (SE)	23.41 (2.50)	9.51 (2.49)	10.42 (2.50)	-1.30 (3.07)
95% Confidence Interval	18.48 ; 28.34	4.61 ; 14.40	5.49 ; 15.35	-7.33 ; 4.74
Difference Estimate (SE)	-	13.90 (3.53)	12.99 (3.54)	24.71 (3.96)
95% Confidence Interval	-	6.95 ; 20.85	6.02 ; 19.96	16.92 ; 32.50
p-value	-	<0.001	<0.001	<0.001

Figure 1: Time-adjusted $SPID_{48}$ up to first dose of rescue medication.



5.2 Pharmacokinetic properties

Absorption

Combodex IV is administered as a 15-minute infusion, and the peak plasma concentration of each drug is reached at the end of the infusion. The two active drugs in Combodex IV reach peak plasma levels in the same time frame and have similar plasma half-lives (paracetamol 2.39 ± 0.27 hours, ibuprofen 1.88 ± 0.28 hours).

The pharmacokinetic parameters of Combodex IV, as determined by a study in 29 healthy volunteers, are presented in Table 2.

Table 2: Mean (SD) pharmacokinetic parameters of paracetamol and ibuprofen in each treatment group.

	Treatment (Mean ± SD)			
Paracetamol	**Combodex IV IV infusion, 15 min**	**Paracetamol IV IV infusion, 15 min**	**Combodex IV Half dose IV infusion, 15 min**	**Combodex Caplets Oral caplet**
C_{max} (ng/mL)	26709.57 ± 5814.74	26236.06 ± 5430.52	12880.39 ± 2553.15	14907.16 ± 6255.10
AUC_{0-t} (ng.h/mL)	37553.97 ± 9816.96	35846.20 ± 8734.15	18327.40 ± 4758.34	34980.80 ± 9430.21
$AUC_{0-\infty}$ (ng.h/mL)	39419.95 ± 10630.63	37651.43 ± 9454.60	19337.01 ± 5146.46	37023.82 ± 10388.31
T_{max} (h)	0.25 (end of infusion)	0.25 (end of infusion)	0.25 (end of infusion)	0.73 ± 0.42
$t_{1/2}$ (h)	2.39 ± 0.27	2.38 ± 0.25	2.44 ± 0.25	2.51 ± 0.33
Ibuprofen	**Combodex IV IV infusion, 15 min**	**Ibuprofen IV IV infusion, 15 min**	**Combodex IV Half dose IV infusion, 15 min**	**Combodex Caplets Oral caplet**
C_{max} (ng/mL)	39506.69 ± 6874.06	40292.97 ± 7460.04	20352.05 ± 3090.87	19637.38 ± 5178.29
AUC_{0-t} (ng.h/mL)	73492.69 ± 16509.61	72169.59 ± 15608.70	39642.48 ± 9679.16	70417.75 ± 16260.16
$AUC_{0-\infty}$ (ng.h/mL)	74743.31 ± 17388.69	73410.65 ± 16500.76	40333.88 ± 10240.30	72202.48 ± 17445.46
T_{max} (h)	0.25 (end of infusion)	0.25 (end of infusion)	0.25 (end of infusion)	1.49 ± 0.89
$t_{1/2}$ (h)	1.88 ± 0.28	1.87 ± 0.27	1.88 ± 0.30	1.99 ± 0.36

Note: Combodex caplets = paracetamol 500 mg/ibuprofen 150 mg film-coated tablets.

Pharmacokinetic parameters were similar following a single dose of Combodex administered either intravenously or orally, except the C_{max} of the intravenous formulation was twice that of the oral formulation and, as expected, the T_{max} following intravenous administration was achieved much faster(in 15 minutes) than with the oral formulation.

Distribution

Paracetamol is distributed into most body tissues. Ibuprofen is highly bound (90-99%) to plasmaproteins.

Metabolism

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less than 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liverdamage.

Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

In a single dose clinical study, the effect of ibuprofen on the oxidative metabolism of paracetamol wasevaluated in healthy volunteers under fasting conditions. The study results indicated that ibuprofen didnot alter the amount of paracetamol undergoing oxidative metabolism, as the amount of paracetamol and its metabolites (mercapturate-, cysteine-, glucuronide- and sulfate-paracetamol) were similar whenadministered alone, as paracetamol, or with the concomitant administration of ibuprofen (as a fixed combination).

Elimination
Paracetamol elimination half-life varies from about 1 to 3 hours.
Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hoursof ingestion. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

5.3 Preclinical safety data

In single and repeat-dose toxicity studies conducted in rats, co-administration of paracetamol and ibuprofen at a ratio matching that in Combodex IV (i.e., at a paracetamol-to-ibuprofen ratio of 3.3-to-1) and at dose levels approximately equal to those that patients would receive when using Combodex IV at the maximum recommended dose did not increase the risk of GI or renal toxicity.

The effect of single intravenous or perivenous doses of Combodex IV in an acute local irritation study in male rabbits showed that Combodex IV has little potential to produce local irritation when administered intravenously at the recommended dose level. Moreover when conducting an *in vitro* blood compatibility assessment,no additional haemolysis, plasma protein flocculation/precipitation or platelet aggregation was observed with Combodex IV than with paracetamol IV or ibuprofen IV alone.

Ibuprofen
The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastro-intestinal tract. *In vitro* and *in vivo* studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found. Ibuprofen led to inhibition of ovulation in rabbits as wellas disturbance of implantation in various animal species (rabbit, rat, mouse). Experimental studies havedemonstrated that ibuprofen crosses the placenta. For maternally toxic doses, an increased incidence ofmalformations (ventricular septal defects) was observed. Environment risk assessment studies have shown that ibuprofen may pose a risk for the aquatic compartment, especially fish.

Paracetamol
Paracetamol in hepatotoxic doses showed genotoxic and carcinogenic potential (liver and bladder tumours), in mice and rats. However, it is considered that this genotoxic and carcinogenic activity is related to changes in the metabolism of paracetamol when in high doses/concentrations and does not represent a risk for the clinical use.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Cysteine hydrochloride monohydrate
Disodium phosphate dihydrate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze. Protect from light.

6.5 Nature and contents of container

Combodex IV is supplied in 100 ml clear, Type II glass vials, closed with a grey bromobutyl rubber stopper and an aluminium flip-off cap, in a pack size of 10 vials.

6.6 Special precautions for disposal and other handling

Visually inspect Combodex IV for particulate matter and discolouration prior to administration, whenever solutionand container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.

In the absence of compatibility studies, this medicine should not be mixed with diluents. If less than a full vial is required for a single dose, the correct amount should be infused and the remaining solution discarded (see also section 4.2).

Combodex IV should be used in one patient on one occasion only. It contains no antimicrobial preservative. Any unused solution should be discarded.

This medicinal product may pose a risk to the environment (see section 5.3).
Any unused solution should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER(S)

168-56-36312-00

Revised in May 2025 according to MOH guidelines