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EXPERT REVIEW REPORT

MEDICAL SAFETY OF IVERMECTIN

As per the request of MedinCell SA (France), I the undersigned certify to have perused the publicly available information relevant to conduct an extensive analysis of ivermectin safety in human beings. The aim of the present review is to propose an independent, evaluative judgement of this information which includes original scientific publications and literature reviews, case reports, and any other source provided it can be undisputedly tracked down and freely accessed. The author personally collected and reviewed all the cited information from the beginning of September 2020 to the end of February 2021.

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I. EXECUTIVE SUMMARY

Ivermectin was first approved as a human medicine in 1987. In addition to 40 years of extensive use as a veterinary medicine, it has been prescribed to hundreds of millions of human beings worldwide to prevent or treat a variety of parasitic diseases. Recently, the anti-SARS-cov-2 activity of ivermectin became the focus of numerous experimental studies and clinical trials, the results and interpretation of which generated a vigorous and still ongoing debate to establish how effective ivermectin is or could be against COVID-19. Drug approvals by regulatory authorities rely on a risk-benefit analysis. Benefit is assessed from clinical trials conducted in full compliance with guidelines. Severe adverse reactions are often too rare to enable clinical trials to generate accurate quantitative incidence data. Pharmacovigilance (or post-marketing drug surveillance) is another essential source of information on drug safety. The aim of this expert review report is to propose an independent and fair assessment of ivermectin medical safety profile based on an extensive analysis of the publicly available information (over 500 articles and web sources) taking into account known limitations and uncertainties at the time of writing.

The assessment of reported adverse events temporally associated with ivermectin treatment shows that the adverse effects of ivermectin used to be infrequent (< 2-5% of treated patients) and mild to moderate. They mainly consisted of dizziness, tremor, tingling and sleepiness; fever, fatigue and headache; nausea, abdominal pain and diarrhea; transient tachycardia and orthostatic hypotension; pruritus and rash. More severe neurological complications (e.g., seizures, confusion, encephalopathy) are possible, but rare. They essentially developed in susceptible individuals, particularly in patients with a severe form of a parasitic disease, such as Onchocerciasis or Loa-Loa microfilariasis. A sudden and marked drop in blood pressure, severe skin reaction and liver injury have been mentioned in early safety reviews. The clinical experience accumulated over the years showed these severe adverse events are unequivocally extremely rare. The often-reiterated claim, even today, that ivermectin can be lethal in treated patients only rests on a one-page correspondence to the Lancet published in 1997. This claim is deemed to be unfounded as it has never been further substantiated until today and instead,

subsequent publications repeatedly showed this claim was either incorrect or methodologically inaccurate.

Patients may indeed die after taking ivermectin. It is clear that they most often suffered from a severe form of parasitic disease so that death can hardly be considered to be due to ivermectin direct toxicity and instead to be a likely consequence of insufficient ivermectin efficacy against a huge parasite load. The majority of those recorded adverse events that were neither moderate nor rapidly recovering spontaneously are therefore linked to ivermectin effects on the target parasites and thus reflect the exposed host's reaction to the death, alteration and/or expulsion of these parasites instead of any direct toxic effects of ivermectin on treated human beings as further evidenced by the low-grade severity of acute poisonings either suicidal or accidental human exposure. Last but not least, poor health conditions and comorbidities preexisting to ivermectin treatment are recognized to be critically contributive.

The results of nonclinical toxicology studies conducted by Merck & Co prior to the first approval of ivermectin as a human medicine supported the allegation that a suitable safety level was likely to be achieved in treated humans. This was confirmed with the rapidly expanding therapeutic use of ivermectin over 3 decades. Nevertheless, several initial nonclinical studies were compatible with the conclusion that ivermectin could prove to be a human teratogen as well as a more potent toxicant in infants and elderly people. The positive clinical experience accumulated with ivermectin in pregnant women is leading a growing number of medical experts to break away from early adamant contra-indications. That ivermectin might be more toxic in infants was hypothesized based on the results of nonclinical studies comparing ivermectin toxicity in young adult and infant either in rats or monkeys. The currently available information in humans does not support these animal findings. Ivermectin was conclusively shown to interfere with drug specific transporters in the gut and the blood-brain barrier. This could have been the clue to the claimed greater toxicity of ivermectin in infants, if it had ever been confirmed clinically. Likewise, no greater toxicity of ivermectin has been substantiated in elderly people despite assertions that an ageing blood-brain barrier might lead to increased ivermectin levels in the brain. That ivermectin is routinely used throughout the world to treat scabies in elderly people without major safety issues is noteworthy. For the time being, the role of the blood-brain barrier, if any, in the

occurrence of ivermectin-induced adverse effects is deemed to be at least ill-documented. Several national pharmacovigilance networks and international organizations released information or opinions ascertaining ivermectin safety in human subjects treated with parasitic diseases. Likewise, no severe adverse reactions have seemingly so far been described in relation to off-label studies or clinical trials of ivermectin as a potential prophylactic or curative treatment of COVID-19.

In any case, the clearly positive conclusions of the present analysis as regards the medical safety profile of ivermectin will have to be confronted, as is common practice for any new drug or official therapeutic indication, to the data accumulated by state-of-the-art post-marketing surveillance, should ivermectin be recommended for use in non-parasitic diseases, such as COVID-19.

II. INTRODUCTION

Ivermectin is a semisynthetic derivative of the avermectin family of macrocyclic lactones, a class of antiparasitic agents obtained from the fermentation products of the microorganism *Streptomyces avermitilis*, an actinomycetes isolated in a Japanese soil sample by the Kitasato Institute in Tokyo [Omura, 2016]. Ivermectin development started in 1975 at Merck & Co in the USA, and it was approved for veterinary use in 1981 (brand name: Ivomec®). The French Ministry of Health was the first regulatory authority to approve ivermectin as a human medicine (brand name: Mectizan®) in 1987. The US FDA approved oral ivermectin in 1996 (brand name: Stromectol®). Today, a number of veterinary and human generics are commercially available. In 2015, the Nobel Prize of Medicine was presented to William Campbell (Merck & Co), Satoshi Omura (Kitasato Institute) and Youyou Tu (China Academy of Traditional Medicine) for their contribution to the discovery and development of ivermectin.

Ivermectin is a mixture of at least 90% of 22,23-dihydroavermectin B_{1a} (or H_2B_{1a}), and less than 10% of 22,23-dihydroavermectin B_{1b} (or H_2B_{1b}), the molecular weight of which is 875.10 and 861.07, respectively [Fisher & Mrozik, 1989] (fig.1).

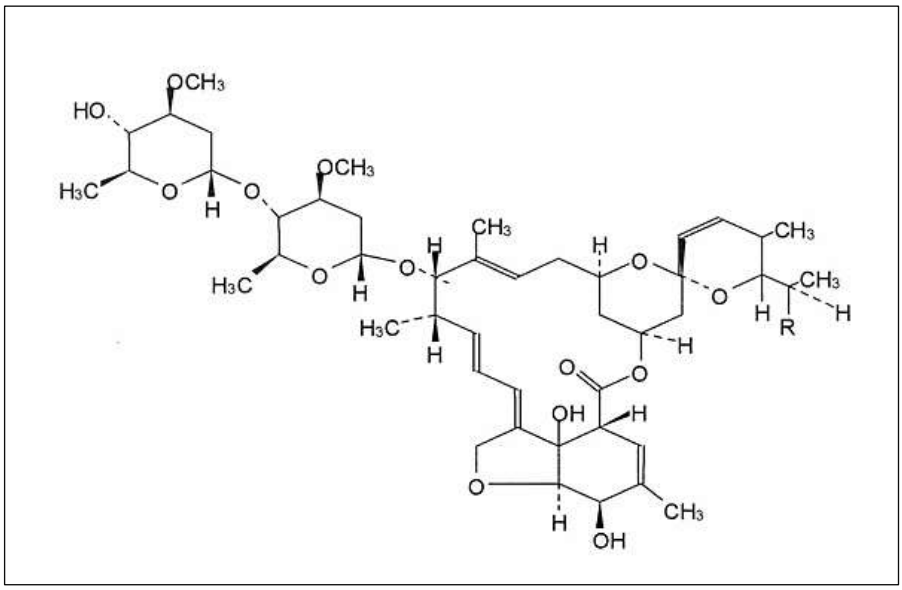

Figure 1: *Chemical structure of ivermectin*

Ivermectin is a potent endo- and ectoparasitic agent with a broad spectrum of activity against nematodes (Ascaris, Trichuris, Ancylostoma), cestodes (Taenia) and trematodes (Fasciola, Schistosoma). It is particularly potent against onchocerciasis (also called river blindness) and loaisis (lymphatic filariasis) [Fox, 2006; Ashour, 2019]. A variety of antiviral activities including SARS-CoV-2 have been described *in vitro* [Caly et al., 2020], but their clinical relevance for the prophylaxis or therapeutic cure of viral diseases including Covid-19 is a matter of ongoing debate [Heidary & Gharebaghi, 2020; Jans & Walstaff, 2020].

Years ago, ivermectin was shown to act as a positive allosteric modulator that selectively opens inhibitory glutamate-gated chloride ion channels resulting in an increased permeability of cell membranes with hyperpolarization of nerve or muscle cells, and ultimately in disruption of the parasite's neural and neuromuscular transmission [Campbell, 1989; Martin et al., 2021]. The greater sensitivity of these GABA-dependent chloride channels towards ivermectin in invertebrates as compared to vertebrates, accounts for the positive safety profile of ivermectin in domestic animals as well as human beings. Alternative mechanisms were subsequently proposed, in particular to substantiate the claimed activity of ivermectin against SARS-CoV-2 and other viruses [Krause et al., 1998; Chen & Kubo, 2018; Changeux et al., 2020; Lehrer & Rheinstein, 2020; Rizzo, 2020; Stokes et al., 2020]. Although more information becomes steadily available on the molecular mechanisms involved in the anthelmintic, antiviral, antimalarial, antimetabolic and anticancer activities of ivermectin, additional mechanisms are being considered but still have to be conclusively established [Laing et al., 2017; Martin et al., 2021]. An attractive hypothesis supported by recent findings underlines the role of interactions between nicotine receptors and ivermectin [Krause et al., 1998; Changeux et al., 2020] to target SARS-CoV-2.

Conflicting opinions have been voiced as regards selection criteria of the optimal dose, treatment regimen or relevant blood levels of ivermectin as a putative anti-COVID-19 drug in human beings, be it proposed as a curative or prophylactic therapeutic tool [Camprubí et al., 2020; Hellwig & Mai, 2020; Peña-Silva et al., 2020; Schmith et al., 2020; Martin et al., 2021]. Although a consensus would be welcome, if and whenever possible, the available information does not pinpoint any clinically relevant difference of ivermectin safety profile according to the therapeutic regimen tested.

Over the years, ivermectin has been, and still is mainly administered by the oral route [Campbell, 1991; Fox, 2006; González et al., 2012] or the topical route [Dourmishev et al., 2005; Zargari et al., 2016]. Other routes of administration include the subcutaneous route [Marty et al., 2005; Pacanowski et al., 2005; Turner et al., 2005; Leung et al., 2008; Fusco et al., 2010], especially in cattle, and far less often the rectal route in human beings [Tarr et al., 2003; Fusco et al., 2010; Bogoch et al., 2015] or the intravenous route in investigative veterinary medicine [Van Amstel et al., 2008; Gokbulut et al., 2010].

Typically, ivermectin is administered as a single dose of 150-200 µg/kg for the treatment of a variety of parasitic diseases. Dosing can be repeated once or twice after a few days, or 3 to 6 months after the last oral dose. The Center for Disease Control (Atlanta, GA) recommend an oral dose of 150 µg/kg on days 1, 2, 8, 9, 15, 22 and 29 in patients with crusted scabies [CDC, 2019]. A number of human studies and randomized clinical trials have been conducted or are ongoing to evaluate the prophylactic or curative activity of ivermectin in COVID-19 (for detailed and updated information, access https://ivmmeta.com). In most instances, the tested dose ranged between 0.2 mg/kg for 1 day and 0.6 mg/kg for 5 days [Kumaraswami et al., 1988; Fox, 2006; González et al., 2012; Navarro et al., 2020; Cepelowicz-Rajter et al., 2021; Hill, 2021]. The safety of repeated daily oral administrations of up to 100 µg/kg ivermectin over 28 days is being evaluated by a randomized, controlled study in human volunteers. At near completion of this study, no safety concern emerged [MedinCell SA, unpublished results].

In humans, the reported elimination half-lives of ivermectin used to range between 12 h and 35 h [US FDA, 1996; González-Canga et al., 2008; JECFA, 2016]. That ivermectin oral bioavailability is 2.6 times higher in fed versus unfed human beings [Guzzo et al., 2002] led to formal recommendations for ivermectin administration. However, clinical data about a food effect on ivermectin pharmacokinetics are scarce. Recent human studies found only minimal [Miyajima et al., 2016], if any food effect (Duthaler et al., 2020).

Ivermectin undergoes limited biotransformation so that most of an oral dose is eliminated unchanged in the feces (from 98% to 99.5% in most animal species). CYP3A4 is the major CYP450 isoform involved in ivermectin biotransformation, followed by CYP2D6 and CYP2E1 to a much lesser extent [Zeng et al., 1999].

No inhibitory effects of ivermectin on CYP450 metabolizing activities have been evidenced in vitro at clinically relevant concentrations. Hydroxylated and demethylated derivatives stand for the majority of identified ivermectin metabolites. Three ivermectin metabolites (M1, M3 and M6) out of the 13 metabolites previously identified after incubation of ivermectin with human liver microsomes were detected in the blood of human healthy volunteers after an oral dose [Tipthara et al., 2021]. These very recently published results have to be confirmed and the role, if any, of these metabolites in the activity and safety of ivermectin further investigated.

Two major features of ivermectin disposition in mammals including man are the role of drug ABC transporters in the gut and the blood-brain barrier. Both features and their relevance for ivermectin safety analysis are discussed later in this report.

III. SUMMARY OF MAIN NONCLINICAL TOXICITY FINDINGS

The majority of publicly available preclinical toxicity findings on ivermectin can be found in a multi-authored book edited by Campbell [1989]. The NDA documentation elaborated by Merck Research Laboratories [US FDA, 1996] and the recently revised evaluation of ivermectin as a veterinary drug residue in food [JECFA, 2016] are other sources of detailed nonclinical information on ivermectin.

- Acute toxicity

Acute (single dose) toxicity studies have been conducted in mice, rats, rabbits, dogs and monkeys. Reported lethal dose 50% (LD_{50}) values are presented in Table I.

The acute toxicity of ivermectin in rodents manifested with ptosis, bradypnea, ataxia, tremors, and loss of the righting reflex. These clinical manifestations were attributed to a direct effect of ivermectin on the central nervous system. Neonatal rats were found to be more severely affected than young adults and this was claimed to reflect the post-natal completion of the blood-brain barrier in this species.

In Beagle dogs, mydriasis was the most sensitive indicator of toxicity. Deaths were preceded by a comatose state. In Rhesus monkeys, the most sensitive indicator of toxicity was vomiting. No tremors or convulsions occurred. No steep dose-response curve was noted in monkeys in sharp contrast to rats.

ROUTE	SPECIES	LD_{50} (mg/kg)
Oral	Mice	25
	Rats	50 (adults) 2-3 (1-2 days old)
	Dogs	80
	Monkeys	> 24
Intraperitoneal	Mice	30
	Rats	55
Dermal	Rats	> 660
	Rabbits	406

Table I. *Reported LD_{50} values in rodents, dogs, monkeys and rabbits* [Campbell, 1989]

- Repeat dose toxicity

The repeated dose toxicity of ivermectin was assessed in a 3-month oral study in mice, a 4-week dermal study and 3- and 6-month oral studies in Sprague Dawley rats, in 3- and 9-month oral studies in Beagle dogs, a 2-week dermal study and a 2-week, 3- and 6-month dermal studies in minipigs, and finally a 2-week oral study in rhesus monkeys [Campbell, 1989; JECFA, 2016]. Estimated NOAEL are presented in Table III.

SPECIES	TREATMENT DURATION	ROUTE	DOSE LEVELS (mg/kg/day)	NOAEL* (mg/kg/day)
Mouse	13 weeks	Dermal	0, 1, 3 and 10	10
Rat	4 weeks	Dermal	0 and 20	20
	13 weeks	Oral	0, 0.1, 0.3, 1.0 and 3.0	3
	13 weeks	Oral	0, 1, 3, 9 and 12	1
	14 weeks	Oral	0, 0.4, 0.8, and 1.6	0.4
	27 weeks	Oral	0, 0.1, 1, 3 and 12	0.1
Dog	13 weeks	Oral	0, 0.1, 0.25, 0.5 and 1.5	0.5
	14 weeks	Oral	0, 0.5, 1 and 2	0.5
	39 weeks	Oral	0, 0.1, 0.5 and 1.5	0.5
Minipig	2 weeks	Dermal	0, 1.6, 3.3, and 13	13
	13 weeks	Dermal	0, 2, 6 and 20	20
	39 weeks	Dermal	0, 2, 6 and 20	20
Monkey	2 weeks	Oral	0, 0.3, 0.6, and 1.2	1.2

Table II. *NOAEL values in repeated dose toxicity studies of ivermectin* [Campbell, 1989]
(*) NOAEL = No Observed Adverse Effect Level

In rats treated orally with 1, 3, 9 or 12 mg/kg/day ivermectin for 13 weeks, mortality was noted at a dose ≥ 9 mg/kg/day. In rats treated orally with 1, 3 or 12 mg/kg for 27 weeks, death preceded by neurotoxic manifestations was observed only in those animals given the highest daily dose. In both instances, mortality was mainly noted in females and during the first two weeks of treatment. No toxicity was noted in rats treated dermally with 20 mg/kg/day ivermectin for 4 weeks

Beagle dogs treated with 0.1, 0.25, 0.5 or 1.5 mg/kg/day ivermectin by oral gavage for 14 weeks developed excessive salivation and decreased body weight at

the highest dose only, and no other significant adverse effects were noted. During another study in Beagle dogs treated orally with 0.5, 1 or 2 mg/kg/day for 14 weeks, 4 out of the 8 dogs from the high dose group had to be euthanized due to neurotoxicity and poor health condition. In contrast, Beagle dogs administered 0.1, 0.5 or 1.5 mg/kg/day ivermectin orally for 39 weeks experienced neither mortality nor marked adverse effects.

Rhesus monkeys did not experience adverse effects after 2 weeks of daily ivermectin administrations. The NOEL (No Observed Effect Level) was determined to be the highest dose level tested (1.2 mg/kg/day).

Finally, no remarkable toxic effects were noted in either mice or minipigs treated daily by the dermal route with up to 13 and 20 mg/kg/day ivermectin, respectively (for 13 weeks in mice and up to 39 weeks in minipigs).

- Genotoxicity

Ivermectin was found negative in a battery of genotoxicity tests performed prior to first approval [Campbell, 1989], including:

- the reverse bacterial mutation test (historical Ames test) using *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100
- the mammalian cell gene mutation assay using the mouse lymphoma cell line L5178Y
- the unscheduled DNA synthesis assay in human fibroblasts
- the rat micronucleus assay *in vivo*.

It is noteworthy that this battery comprised of all the tests required by currently implemented guidelines, in particular guidance S2R1 of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [ICH, 2012].

For the sake of completeness, it has to be mentioned that two academic institutions from Latin America published positive results regarding the genotoxicity and mutagenicity potential of ivermectin either in vitro or following a single subcutaneous administration of 1 mg/kg ivermectin to rats [Molinari et al., 2009; Moreira et al., 2014; Cordeiro et al., 2018]. It is fair to underline that none of these results were generated using fully in-house validated tests or assays conducted in strict

compliance with Good Laboratory Practice rules. No confirmative results have seemingly been reproduced so far.

- Cancerogenicity

The carcinogenicity potential of ivermectin was tested in conventional 2-year bioassays [Campbell, 1989]. Wistar rats were given 0, 1, 3 or 9 mg/kg ivermectin daily by oral gavage. No drug-related tumors were noted in females up to the highest dose and none in males at ≤ 3 mg/kg/day. The multiple of human exposure at 3 mg/kg/day oral dose in male rats in whom no significant treatment-related neoplastic findings were noted, was ≈600. The multiple of human exposure at 9 mg/kg/day dose in female rats, in whom no significant treatment-related neoplastic findings were noted, was ≈2000.

CD-1 mice were administered 0, 0.1, 0.3 and 1% ivermectin cream topically. Non-neoplastic histological findings were noted in the treated skin and lymphoid organs. These were likely to be vehicle-related, but a relationship to the test article could not be ruled out.

- Developmental and reproduction toxicity

Ivermectin was shown to be teratogenic in mice, rats and rabbits when given at repeated doses of 0.2, 8.1 and 4.5 times the maximum recommended human dose, respectively [Campbell, 1989]. Teratogenicity was characterized in the 3 animal species tested. Based on these nonclinical findings, ivermectin was initially classified as a possible human teratogen.

As discussed later in this review, the medical experience accumulated so far following accidental or intentional administration of ivermectin to pregnant women led many regulatory authorities and medical experts to break away from early adamant contra-indications.

Several multigeneration studies have been conducted. In rats, marked parental and offspring toxicity was seen, but no teratogenicity [Lankas et al., 1989]. The role of immature blood-brain barrier in rat pups was hypothesized to be involved. In contrast, no reproductive toxicity whatsoever was noted in dogs treated with 600 µg/kg monthly for 8 months and bred to untreated bitches [JECFA, 2016].

- General and safety pharmacology

When ivermectin was approved as a human medicine for the very first time in 1987, general pharmacology, the precursor of safety pharmacology, was "optional" and not regulated by formal guidelines as safety pharmacology is today. Therefore, limited information is available to document the safety pharmacology profile of ivermectin as briefly reviewed below.

- *Cardiovascular system*

No EKG abnormalities were seen in dogs treated orally with up to 1.5 mg/kg/day ivermectin for 39 weeks. Marked hypotension during nonclinical toxicity studies was only noted in moribund animals treated with ivermectin.

In 32 elderly Liberian men, treated with ivermectin, EKG recording were performed twice daily pretreatment and on five occasions post-treatment. Twenty subjects had pre-treatment EKG abnormalities. Neither significant changes nor new abnormalities were observed [Dukuly et al., 1990].

- *Respiration*

Respiratory disturbances were only noted in moribund animals dosed with ivermectin. No direct effect of ivermectin on the respiratory tract has seemingly been evidenced or suggested.

- *Nervous system*

Neurotoxic effects were the most common adverse manifestations recorded during preclinical studies of ivermectin as already mentioned.

A Serbian research team conducted pharmacology studies to further characterize the central and peripheral effects of ivermectin in rats. Although a single slow intravenous injection of 2.5, 5.0 or 7.5 mg/kg induced no visible CNS depression, sleepiness and staggering were noted during 10 to 40 min after a dose of 10 mg/kg ivermectin, and profound CNS depression leading to death in half of the animals treated with 15 mg/kg. Ivermectin was shown to potentiate thiopentone-induced sleeping time, and this effect was antagonized by pretreatment with flumazenil, an antagonist of benzodiazepine receptors, in agreement with the GABAergic properties

of ivermectin [Trailoić & Nedeljkovik, 2011]. In addition, lidocaine- and strychnine-induced convulsions were antagonized by ivermectin: the anticonvulsive ED_{50} of ivermectin for lidocaine-induced convulsions was 2.44 mg/kg orally, whereas it was higher (4.25 mg/kg) for strychnine-induced convulsions [Trailoić & Varagić, 2007]. In both situations, the anticonvulsive doses were significantly lower than the calculated ivermectin LD_{50} (18.2 mg/kg). Furthermore, flumazenil antagonized the effects of ivermectin only against lidocaine-induced convulsions suggesting that ivermectin produces multiple inhibitory effects in the CNS of mammals via GABA-sensitive and GABA-insensitive mechanisms.

- Local tolerance

The 1% ivermectin cream was found to be irritating to the skin, but not to the eyes of rabbits.

- Immunotoxicity and immune safety

Ivermectin was approved for human use years before the first guidelines relative to immunotoxicity evaluation were published by EM(E)A (2000), the US FDA (2002) and ICH (2005). No extensive evaluation of ivermectin immune safety has so far been conducted using state-of-the-art methods in compliance with current strategies, recommendations or regulatory requirements. As summarized below, the results of several studies, even though their scope was fragmentary, do not lend support to consider ivermectin as an immunotoxicant or a potentially useful immunomodulator.

One early example of immunotoxicity studies typically conducted at the end of the last millennium is the assessment of ivermectin effects on T-dependent and T-independent antibody responses in male CD-1 mice injected subcutaneously only once with 0.2 or 20 mg/kg ivermectin [Blakley & Rousseaux, 1991]. A statistically significant enhancement of T-dependent antibody response was evidenced. Subsequently, Sajid et al. [2007] treated a total of 100 rabbits with 200, 400 or 600 µg/kg ivermectin according to varied schedules. Both humoral and cellular arms of immunity were tested *in vivo* using a panel of reference antigens commonly used several decades ago. When significant "immunoenhancing" findings were noted, the highest dose of ivermectin was most often involved. A third example using a far less conventional model was published by Stankiewicz et al. [1995]. Ten 6-month-old lambs pretreated with ivermectin and

one day later injected with human erythrocytes and ovalbumin were compared to 10 non-pretreated lambs. Cultured lymphocytes from treated animals compared with lymphocytes from control lambs had similar blastogenic responses to concanavalin A or phytohemagglutinin. Similar antibody responses to ovalbumin were seen in both groups.

Experimental studies using animal models of parasitic diseases have been used to evaluate the influence of ivermectin, if any, on immune responsiveness. One typical example refers to the effects of subcutaneous ivermectin on the specific immune response of rabbits infested with mites (*Psoroptes cuniculi*) and rats infested with lice (*Polyplax spinulosa*). Results in rabbits might suggest enhanced immune responses after ivermectin in sharp contrast to negative rat results. The authors concluded that ivermectin had no direct effects on immune responses and that findings in mite-infested rabbits were the consequences of the massive release of antigens associated with the synchronous death of mites [Uhlir & Volf, 1992].

Another important and pending question is whether ivermectin exerts significant anti-inflammatory properties. Decreased or increased levels of pro-inflammatory cytokines have been reported after ivermectin treatment in normal rodents or a few human beings with various parasitic diseases. A detailed review of these results falls beyond the scope of this review. A significant protective effect of ivermectin in acute cytokine release syndromes ("cytokine storms") is highly unlikely. Anti-inflammatory properties were evidenced in a murine model of atopic dermatitis [Ventre et al., 2017]. Indeed, topical ivermectin improved allergic skin inflammation by reducing activation of allergen-specific T cells and the production of inflammatory cytokines.

- Mechanisms of ivermectin toxicity

As mentioned before, all the pharmacological modes of action of ivermectin are not yet fully elucidated and some remain putative. Below is provided a short summary of the current knowledge to help non-specialists understand what is at stake.

- *Role of receptors*

A variety of receptors such as GABA-sensitive and GABA-insensitive chloride channels, nicotinic receptors, Cys-loop receptors, P2X receptors and fernesoid X receptors have been shown or suggested to be involved [Bortolato et al., 2013; Laing

et al., 2017; Chen & Kubo, 2018; Changeux et al., 2020; Martin et al., 2021]. The respective relevance of these possible or putative mechanisms is not fully understood, which is illustrated by quite a few studies and clinical trials attempting to reposition ivermectin beyond approved antiparasitic indications, including anti-inflammatory, anti-viral, immunomodulatory or anticancer indications [Juarez et al., 2018; Martin et al., 2021]. This should plead for avoiding premature assertions regarding the "optimal" dose regimen, the duration of ivermectin treatment or "therapeutic drug levels" as they may prove erroneous, especially when considering non-parasitic medical indications.

From a toxicological point of view, neurotoxicity has been the main safety concern over the years. Today, it is well-established that neurological complications are typically mild to moderate and infrequent in human patients treated with ivermectin, provided they have no underlying parasitic infestation or overt disease [Chandler, 2019; Makenga-Bof et al., 2019]. Ivermectin-induced neurotoxicity has long been linked to GABA-dependent chloride channels [Campbell, 1998]. No significant advance has been seemingly achieved since then in our understanding of ivermectin neurotoxicity.

- *Role of drug transporters*

At the turn of the last century, it became obvious that drug transporters are important factors to consider in the disposition, pharmacological effects and toxicity of drugs. Indeed, they mediate drug uptake into cells and export drugs out of cells. All transporters have a specific pattern of expression in tissues. Those expressed in the small intestine, liver, and kidney may be very important for drug disposition and drug-drug interactions, while those expressed in the blood-brain barrier and maternal-fetal barrier may be expected to protect sensitive tissues from toxic compounds [Daneman & Prat, 2015; Mahringer & Fricker, 2016; Lund et al., 2017; Mayhan & Arrick, 2017].

One of these, P-glycoprotein (P-gp) is a transmembrane protein of the so-called ABC superfamily coded for by the MDR1 gene. P-gp often plays a notable role in the efflux out of cells of drugs, including ivermectin. P-gp is found in enterocytes, capillary endothelial cells that form the blood-brain barrier and the placenta. In the absence of P-gp, ivermectin may be better absorbed from the gastrointestinal tract and may diffuse freely into the central nervous system [Didier & Loor, 1996]. P-gp-deficient animals such as the MDR1a-/- mouse [Schinkel et al., 1996; Geyer et al., 2009] and certain canine breeds such as Collies and Australian, English and White German

shepherds for instance, are highly sensitive to ivermectin neurotoxic potential [Mealey et al., 2001; 2002]. It is noteworthy that the dogs used in nearly all regulatory toxicity studies, namely Beagles, do not carry this deletion. A similar pharmacogenetic predisposition has so far been detected only once in humans, namely a 13-year-old boy who recovered after an acute neurotoxic phase [Baudou et al., 2020]. Last but not least, that mutations of the MDR1 gene are more often seen with drugs, the main biotransformation pathway of which is CYP3A4, has to be taken into account with ivermectin. However, as already mentioned, less than 2% of an oral dose of ivermectin are biotransformed by the CYP450 system so that approximately 98% are excreted unchanged in the feces, which cannot plead for a contributive role of this mechanism.

Despite the huge amount of scientific data accumulated over the last 2 decades, their clinical relevance for human subjects treated with ivermectin remains unclear. Thanks to tremendous advances in biomolecular techniques, an impressive collection of structural details as well as in vitro or in silico results is available. However, whether changes reflecting a spontaneous mutation and/or the influence of a chemical product can reliably predict the occurrence of clinically significative adverse consequences is beyond reach for the time being. It is noteworthy that the currently available human data lend no clear support for any notable impact of ivermectin.

- *Role of the blood-brain barrier*

Drug transporters are present in capillary endothelial cells and constitute the so-called blood-brain barrier. Most, if not all of what is described in the previous section is applicable to the blood-brain barrier. Because of the neurotoxicity of the avermectin pesticides [Yung, 2012; El-Saber et al., 2020; Gueniche et al., 2020], a chemical family to which ivermectin pertains, it was logical to give much attention to the involvement of the blood-brain barrier [Edwards, 2003; Lacher et al., 2015; Chedik et al., 2017]. The greater toxicity of ivermectin manifesting as severe neurotoxic effects and death in immature rats and CF-1 mice has been convincingly associated to minimal P-gp levels in the brain and the jejunum [JECFA, 2016], which at least demonstrates its protective role. Indeed, in sharp contrast to rats [Lankas et al., 1989], neither marked toxicity nor neurotoxic effects were evidenced in repeated dose studies of ivermectin in dogs and monkeys, including multigenerational studies. Interestingly, the blood-brain barrier is known to be mature in newborn dogs, monkeys and humans [JECFA, 2016]. No experimental study has seemingly been conducted so far to

demonstrate in clinically relevant conditions that ageing animals are more sensitive to ivermectin. As summarized later in this report, the claim that elderly people are at a greater risk of neurotoxic effects directly caused by ivermectin is not substantiated by the available clinical data.

IV. HUMAN ADVERSE EVENTS AND IVERMECTIN EXPOSURE

Since the 1980s, ivermectin has been used worldwide for the treatment of parasitic diseases, first in animals and then in human beings. Although an accurate estimate is probably not achievable, the consensus is that hundreds of millions of human beings have already been given ivermectin either prophylactically or curatively [Thylefors, 2008]. The total number of doses distributed during the last 30 years has even been claimed to be equal to one third of the present world human population [Chaccour, 2020].

- Adverse events in clinical trials and following medical prescription of ivermectin

A large number of clinical reports and review papers describing adverse events during a clinical trial or after a medical prescription of ivermectin have been published over the last 3 decades.

Typically, mild to moderate adverse effects of ivermectin consist of diarrhea, nausea, abdominal pain, tingling, burning sensation, fever, fatigue, headache, and sleepiness [Addiss et al., 1991; Aziz et al., 1982; De Sole et al., 1989; Whitworth et al., 1991; Burham et al., 1993; Kamgno et al., 2004; Kircik et al., 2016; Budge et al., 2018; Shouman et al., 2020]. They are most often infrequent (usually recorded in less than 5% of human beings treated with ivermectin either prophylactically or curatively). They generally do not necessitate stopping ivermectin or withdrawing volunteers from clinical trials.

- *Deaths*

In 1997, Barkwell and Shield reported the death of 15 among 47 residents with scabies from a long-term care facility after being treated by topical applications of the pesticides crotamiton and lindane, and 3 months later with a single oral dose of 150-200 µg/kg ivermectin. When comparing to several groups of residents from the same facility not treated by ivermectin, the authors claimed having found a highly significant statistical difference. Although they did not describe any specific sequence of events leading to death, they concluded that ivermectin was the causative agent.

This one-page correspondence to the Lancet set off a long-lasting debate. Shortly afterwards, Diazgranados and Costa (1997) reported their own experience that no excess mortality was found in a cohort of Columbian patients with scabies despite repeated ivermectin administrations for months or even years. Subsequently, no statistically significant excess in death rates among Papua New Guinea patients with scabies was found when comparing patients treated with diethylcarbamazine associated with ivermectin, or not [Alexander et al., 1998].

Remarkably, Barkwell and Shield (1997) did not refer to any relevant information available at that time. Among 50 929 persons from West Africa treated with ivermectin, none was reported to have died during the 72-hour post-treatment period [De Sole et al., 1989]. One 38-year-old female patient in poor health condition died at day 10 post-ivermectin but a pre-existing parasitic co-morbidity was considered to be involved. Ivermectin was also given as a single oral dose of 150 µg/kg twice one year apart to 14 000 workers of a rubber plantation in Liberia. Compliance to treatment was 97%. Neither deaths nor severe adverse reactions were reported and 0.5% of treated human subjects developed moderate adverse effects [Pacqué et al., 1990].

More recently, no deaths attributable to ivermectin treatment were recorded in patients with onchocerciasis during a 3-year randomized controlled trial conducted in Cameroon. In total, 7237 treatments were given, including 2808 doses of placebo; 2226 doses of ivermectin at 150 µg/kg, 475 doses at 400 µg/kg and 1728 doses at 800 µg/kg [Gardon et al., 2002]. Finally, Kinyanjui et al. (2018) revisited Barkwell and Shield's results using a novel framework model of scabies and a Bayesian approach. They concluded there was no statistical evidence for any excess of deaths.

Based on all the data presented above, the author of this report believes it is fair to say that ivermectin did not directly induce an excess of deaths in treated groups of human subjects. Statements, past or present, that ivermectin can kill patients, are therefore considered to be misleading as they do not take into account all the medical information that has been accumulated over the last decades.

- <u>Adverse events listed by main affected organ or system</u>

Neurological adverse events

Central and peripheral neurological manifestations during ivermectin treatment are the most frequent adverse events. Tingling, headache, dizziness, sleepiness and

tremor are the most common, mild to moderate adverse events associated with ivermectin administration.

- Seizures have been reported among severe neurological events associated with ivermectin treatments. In fact, ivermectin was found to exert anticonvulsant effects in a few animal models. More importantly, a progressive decrease in the incidence of convulsions was reported in populations affected by onchocerciasis after starting ivermectin treatment [Kipp et al., 1992; Fodjo et al., 2018].
- Full-blown encephalopathy is the most severe neurological complication of ivermectin treatment. Because of its severity, it attracted a lot of concern regarding ivermectin safety. Although the mechanism involved is not fully elucidated, it is widely agreed today that encephalopathies associated with ivermectin treatment are most often seen in patients with onchocerciasis or Loa Loa filariasis so that the risk of severe encephalopathy directly linked to ivermectin in patients without any of these pathological conditions is likely to be very small [Dukuly et al., 1990; Boussinesq et al., 1998; Gardon et al., 2003; Twum-Danso, 2003a; 2003b; Kamgno et al., 2008; Chandler, 2018; Chesnais et al., 2020]. Be it very small, however, this risk does not allow to exclude the possibility for ivermectin to cause encephalopathy after a recommended treatment regimen [Massi et al., 2017] or in relation to an accidental or suicidal overdose, as discussed later in this report.

Gastrointestinal adverse events

Diarrhea, nausea and abdominal pain are the most frequent gastrointestinal adverse events linked to ivermectin administration. As indicated above they are usually mild to moderate and seen in a few percent of treated subjects.

No severe adverse reaction affecting the gastrointestinal system has seemingly been attributed to ivermectin.

Dermatological adverse events

Rapidly resolving rash and maculopapular skin eruptions can be seen after ivermectin intake. Severe dermatological complications including toxic epidermal necrosis (TEN), the Stevens-Johnson syndrome (SJS), bullous pemphigoid-like eruption, the drug reaction with eosinophilia and systemic symptoms (DRESS) and drug fixed eruption have been reported in very few patients treated with ivermectin

[Mara et al., 2004: Nakamura et al., 2006; Fujimoto et al., 2014; Aroke et al., 2017; Kerneuzet et al., 2018; Ngwasiri et al., 2018].

Oshikoya et al. (2020) reported 24 015 adverse drug reactions recorded by the Nigerian Pharmacovigilance Center from 2004 and 2017. Of these, 284 were severe toxidermias. Anti-HIV drugs were the leading cause. Ivermectin was suspected to be involved in one case. Up to now, no toxidermia has seemingly been described in patients treated prophylactically with ivermectin.

The Mazzotti reaction is a moderate to severe adverse event characterized by a variety of dermatological, cardiovascular and systemic symptoms including fever, chills, swollen and tender lymph nodes (lymphadenitis), headache, myalgia, arthralgia, tachycardia, hypotension and/or shock, ocular and skin manifestations. The latter include pruritus, papules, edema, wheal, vesicles and pustules together with scales, excoriation, erosion, ulcer and crusts. It has been mainly, if not only described in patients after the first dose of diethylcarbamate or ivermectin to treat onchocerciasis [Awadzi & Gilles, 1992; Ito, 2013]. Available data give little support to either a complement-mediated or immediate hypersensitivity. Eosinophil degranulation with subsequent release of inflammatory mediators into the tissues and peripheral blood has been hypothesized [Ottesen, 1987]. No direct toxicity of either diethylcarbamate or ivermectin is deemed to be involved, but instead the acute destruction of microfilariae.

Mazzotti reactions can be severe. Based on purely clinical observations, the diagnosis may erroneously lead to suspect a drug-induced anaphylactic or pseudo-allergic reaction, or a cardiovascular collapse shortly after the first administration of ivermectin. The direct causative role of ivermectin is unlikely as Mazzotti reactions have seemingly never been reported in ivermectin-treated patients not suspected of underlying onchocerciasis, such as COVID-19 patients.

Cardiovascular adverse events

Cardiovascular adverse events in ivermectin-treated human subjects have been seldom reported. Limited information is available on the human cardiovascular safety of ivermectin. Thirty-two elderly Liberian men were treated with ivermectin and electrocardiograms (EKG) were performed twice daily pretreatment and on five occasions post-treatment. Twenty subjects had pre-treatment EKG abnormalities No

significant changes and no new abnormalities were observed following ivermectin administration.

As mentioned above, brutal hypotension can occur in the very early phase of ivermectin treatment in patients with onchocerciasis [De Sole et al., 1989].

Hepatic adverse events

Ivermectin was suspected to be a hepatotoxicant. In fact, this claim reproduced in several publications was based on few individual case reports [Sparsa, 2006; Veit et al., 2006; Hirota et al., 2011] where the causal relationship with ivermectin treatment was not convincingly established. The last update of LiverTox [2018], a database of drug-induced hepatotoxicity, did not classify ivermectin as a known hepatotoxicant, a conclusion recently confirmed by the US National Institutes of Health [NIH, 2021].

Hypersensitivity/allergy

"Drug allergy" is a complex and ill-understood area. Despite remaining uncertainties, it can be judged that hypersensitivity reactions (a much better term than allergy) to ivermectin are very uncommon in treated patients. Indeed, skin rash, Quincke's edema, anaphylactic shock or allergic contact dermatitis have been very rarely, if ever recorded in ivermectin-treated human subjects.

No hypersensitivity reactions were recorded among 4 groups of 50 Liberian patients with onchocerciasis treated with an oral dose of 0, 100, 150 or 200 µg/kg ivermectin either once or at 6,12-month intervals. Only mild to moderate systemic reactions linked to onchocerciasis were noted [Greene et al., 1991]. That an anaphylactoid reaction may occur as a consequence of the parasite destruction by ivermectin in patients pre-sensitized to onchocerciasis antigens has been suggested to occur. Accordingly, such systemic reactions are not expected to develop in human subjects without an ongoing parasitic disease, such as subjects to be prophylactically treated with ivermectin against COVID-19.

Flu-like reactions with fever, chills, joint pains, nausea, rash have long been reported shortly after ivermectin intake. They have typically been mild to moderate. To reconcile these clinical findings with data that ivermectin can decrease IL-1 and IL-6 levels, it is tempting to assume these flu-like reactions may reflect the inflammatory reaction due to ivermectin-induced killing of Onchocerca microfilariae.

Respiratory adverse effects

No direct effect of ivermectin on the respiratory system has seemingly been reported so far.

Hematological and lymphoid adverse effects

Mild to moderate lymphadenopathies have been reported, but they seem to be restricted to patients with Onchocerciasis (Mazzotti reaction).

Inconsistent, mild to moderate and spontaneously relapsing changes in hematological parameters and coagulation have been reported, in particular prolongation of prothrombin time without bleeding [Homeida et al., 1988; Pacqué et al., 1989; Richards et al., 1989; Hay & Arnott, 1990; Whitworth et al., 1992].

No severe hematological adverse reactions associated with ivermectin have seemingly been reported so far. Two male patients developed hematomas 4 weeks after taking a single dose of 150 µg/kg ivermectin that spontaneously recovered within a few days [Homeida et al., 1988].

Ototoxic adverse effects

In their recent review of the ototoxicity of potential COVID-19 drug treatments, Little and Cosetti [2021] confirmed the occurrence of tinnitus and vertigo associated with ivermectin intake. However, these adverse effects were typically mild to moderate and rapidly resolving. No direct and long-lasting otoxicity associated with ivermectin has seemingly ever been described.

- **Acute poisonings and accidental overdoses**

A suicidal intake of ivermectin was reported in a 19-year-old woman with severe Loa-Lao filariasis. She developed nausea and vomiting, and moderate neurological manifestations including ataxia, reactive mydriasis and hyperreflexia after possibly ingesting 100 times the recommended therapeutic dose (≈400 3-mg ivermectin tablets). She received conventional supportive treatment and could be discharged from hospital on day 4 post-ingestion [Djeunga et al., 2019].

Only very few cases of accidental human overdose have been reported despite the wide availability of ivermectin as a veterinary and human medicine [Hall et al., 1985; Graeme et al., 2000; Deraemecker et al., 2014; Goossens et al., 2014]. Usually,

moderate neurotoxic manifestations with rapid recovery after unspecific supportive measures were the predominating course of events. No accidental overdose including in infants and young children had a lethal outcome.

Two lines of ivermectin data from veterinary medicine practice deserve particular attention. Firstly, acute intoxications (often called "ivermectin toxicosis") have long been reported in dogs and cats [Merola & Eubig, 2018]. They are thought to be often due to the inadvertent administration of an excessive dose by the animal's owner even though an exaggerated sensitivity of dogs and cats to ivermectin may also be involved. Such an exaggerated sensitivity has been well documented in Collies and a few closely related breeds [Hopper et al., 2002]. The multi-drug-resistance gene (MDR1) encodes P-glycoprotein (P-gp), a large transmembrane protein that is an integral part of the blood-brain barrier. A deletion mutation of the MDR 1 gene was shown to be associated with ivermectin sensitivity. Animals that are homozygous for this mutation display the ivermectin-sensitive phenotype. Between one third and one half of collies were found to bear the ivermectin-sensitive phenotype [Mealey et al., 2001; 2002]. A similar mutation was identified in few cats [Mealey & Burk, 2015].

For a balanced interpretation of these findings, it is noteworthy to mention that severe adverse effects have repeatedly been described in Collies administered a usually safe dose of several approved veterinary medicines such as vincristine [Lind et al., 2013], apomorphine [Campbell et al., 2017], loperamide [Sartor et al., 2004] and acepromazine [Deshpande et al., 2016]. Another interesting information derived from the veterinary medicine practice is the demonstrated efficacy of intralipid emulsions to treat ivermectin toxicosis in dogs [Fernandez et al., 2011] as this is an increasingly recommended supportive measure for the management of severe human poisonings of varied causes.

The acute human toxicity of avermectins and related compounds such as abamectin, when used as pesticides is well-characterized. Acute poisonings with avermectins, although rare, can be lethal [Chung et al., 1999; Soyuncu et al., 2007; Sung et al., 2009; Bansod et al., 2013; El-Saber et al., 2020]. Markedly different modalities of exposure between avermectin pesticides and ivermectin – as an approved antiparasitic drug – can reasonably be claimed to account for the better safety profile of the latter.

V. RISK FACTORS

- **Clinical safety of ivermectin in infants and children**

Ivermectin was found to be markedly more toxic in infant rats than in young adults. The blood-brain barrier being immature in newborn rats for several weeks, the hypothesis was made that a facilitated passage of ivermectin into the brain could explain this increased toxicity [Lankas et al, 1988]. Although this hypothesis has been so often reiterated that it might be thought of as a sort of scientific evidence, no clinically proven susceptibility of human infants and children to ivermectin has been consistently reported.

The last revision of the model list of essential medicines published by the World Health Organization includes oral ivermectin for children [WHO, 2019]. However, ivermectin is very inconsistently approved for therapeutic use in children less than 15 kg. The results of several off-label studies showed that ivermectin is likely to be safe as well as effective in infants and young children.

No adverse effects were seen among 18 children given one single dose of ivermectin to treat scabies [Del Mar Sáez de Ocariz, 2002]. Chosidow and Gendrel [2015] reported that 200 mg/kg ivermectin orally twice at one week apart was effective in most infants weighing <15 kg and induced infrequent and rare adverse effects. Their results confirmed the earlier findings of Becourt et al. [2013] in 15 children. Levy et al. [2020] collected the medical data relative to 170 children aged 1-64 months (weight: 4-14.5 kg) treated for scabies with a mean dose of 223 µg/kg (and a second dose in 89% of cases). Adverse events (none of which were serious) were reported in 7 children. Very similar findings have been repeatedly reported [Wilkins et al., 2018; Wimmersberger et al., 2018; Colebunders et al., 2019; Morris-Jones, 2020; Ständer et al., 2020].

Last but not least, the putative anticancer effects of ivermectin were tested for humane reasons in 3 children with unmanageable acute myelogenous leukemia at the daily dose of 1 mg/kg by continuous infusion for 15 days to 2 children aged 11 and 13 years, and for 6 months to another child aged 5 years. The authors concluded that ivermectin induced no serious adverse effects [Galvao de Castro, 2020].

- **Clinical safety of ivermectin in pregnant and breast-feeding women**

Despite early preclinical findings, no malformation temporarily associated with ivermectin exposure of pregnant women have seemingly ever been recorded or suspected. Similarly, no immediate or long-term adverse consequences on infants and children exposed to ivermectin via their pregnant mother have been recorded or suspected [Gyapong et al., 2003; Pacqué et al., 1990; Nicolas et al., 2020; Westlake & Aronoff, 2020].

The malformative or generational risk of medicines has long been shown to generate a negative perception in the general population. This negative perception explains the critical level of medicolegal concern associated with rightly or wrongly suspected consequences. It is very hard to unquestionably address these issues and provide undebated (more than undebatable) answers. Recently, the US Food and Drug Administration (FDA, 2019) proposed new methodological approaches that could be instrumental to help revise rather conservative regulatory decisions.

There is only scarce data on breast-feeding women treated with ivermectin. Measured ivermectin levels in milk were found to be very low [Ogbuokiri et al., 1993; Rodari et al., 2020]

- **Clinical safety of ivermectin in the elderly**

Elderly people have repeatedly been claimed to be at a greater risk of ivermectin-induced neurotoxicity. However, such a claim is based on theoretical considerations which have so far not been convincingly demonstrated to be correct by a variety of clinical findings [Raffi et al., 2019].

That the blood-brain barrier, as a sort of global entity, can be disturbed with ageing is hardly disputable. That the blood-brain barrier is a complex entity comprising of many components, the precise role of which and their respective interactions is far from being fully established from a clinically significant perspective, is undisputable as well.

- **Comorbidities**

  - *Parasitic diseases*

There is a large body of evidence that ivermectin-associated adverse reactions are more frequent and more severe in patients with onchocerciasis or Loa Loa filariasis [Dukuly et al., 1990; Boussinesq et al., 1998; Gardon et al., 2003; Twum-Danso, 2003b; Chandler, 2018; Chesnais et al., 2020]. Although the mechanism is not completely elucidated, the exposed host's reaction to the death, release and/or expulsion of the targeted parasites as a consequence of ivermectin pharmacological effects is believed to be involved by most authors.

Possibly contributive pathogenic mechanisms may include embolic vascular pathology accompanied by local inflammation, hereditary abnormalities of the blood brain barrier MDR1/ABCb1 gene, or genetic predisposition to excessive inflammatory responses [MacKenzie et al., 2003], but so far, no conclusive demonstration has been provided.

- *Immunosuppression*

Ivermectin has not been conclusively shown to exert effects on immune responsiveness potent enough to facilitate the development of infectious complications in immunodepressed human patients.

- *COVID-19*

At the time of writing, ivermectin was approved as a prophylactic and/or curative treatment of COVID-19 in a limited number of countries, for instance Belize, Bolivia, Columbia, Moldavia, Zimbabwe… In addition to an ongoing meta-analysis of randomized, controlled clinical trials with the aim to provide the awaited reliable data necessary to substantiate further regulatory decisions [Hill et al., 2021], a number of investigative human studies and poorly controlled clinical trials have been or are being conducted. A frequently revised list can be accessed at https://ivmmeta.com.

It is beyond the scope of this review to provide a description of all available results. Let it be said that globally well above 10 000 human subjects have been enrolled in investigative studies or clinical trials. Although the treatment regimen, the dose, the duration of follow-up, the type of treatment (curative or prophylactic), were variable, the majority of sources provide suitable contributions for assessing the medical safety of ivermectin. Although the incidence of mild to moderate adverse events may vary across studies, a very low incidence of severe ivermectin-induced adverse effects was consistently reported.

It is of note that neither deaths nor severe adverse events attributable to ivermectin have been reported. An illustrative recent report was published by Alam et al. [2020].

- *Drug associations*

Ivermectin has been shown to act as a strong inhibitor of p-glycoprotein [Bartley et al., 2009; Didier & Loor, 1995, 1996; Lespine et al., 2006; 2007; 2009; Jani et al., 2011; Ballent et al., 2016; Merola et al., 2018]. It also inhibits CYPA4 [Zeng et al., 1998; Kellerova et al., 2019] and is extensively bound to plasma proteins [Klotz et al., 1990]. All 3 mechanisms can potentially (or theoretically) lead to clinically significant drug interactions. Actually, very few clinical reports of a significant drug interaction with ivermectin have been published so that in most instances, only assumptions can be made from pharmacokinetic evaluation of specific drug interactions in humans or in animals [Guéniche et al., 2020].

- *Anticoagulants*. Although the possible interaction of ivermectin and warfarin is often mentioned, only one case report of a clinically significant interaction has ever been published [Gilbert & Slechta, 2018]. As previously mentioned, early findings that ivermectin might adversely influence coagulation were recently contradicted. No significative risk for such an interaction is demonstrated.

No clinical study to investigate the risk of drug interactions between ivermectin and heparin within the context of COVID-19 treatment has so far been published [Horowitz & Freeman, 2020].

- *Antimicrobials*. A number of mainly pharmacokinetic studies in animals evaluated possible interactions with erythromycin [Bohlen et al., 1995], azithromycin [El-Tahtawy et al., 2008], cetirizine [Olsen et al., 2007], doxycycline [Agbedanu et al., 2015; Atlam et al., 2020], ketoconazole [Alvinerie et al., 1998: Hugnet et al., 2007], itraconazole [Bellent et al., 2007], and rifampicin [Ballent et al., 2010]. No clinically significant interactions have been described either in animals or humans.

- *Antiparasitic drugs*. No pharmacokinetic interaction was found in human subjects treated with albendazole and ivermectin [Awadzi et al., 2003] or levamisole and ivermectin [Awadzi et al., 2004].

- *CNS drugs.* Similarly, the following studies failed to evidence any clinically relevant interactions between ivermectin and phenobarbital [Ballent et al., 2010], tramadol [Ferreira da Cruz et al., 2020], antiepileptics [Grewal et al., 2017], loperamide [Lifschiyz et al., 2004] and trifluoroperazine [Marques-Sanros et al., 1999]

- *Miscellaneous*: the same conclusion applies to results dealing with putative interaction between ivermectin and dexamethasone [Areskoga et al., 2008], cyclosporin [Marques-Sanros et al., 1999], verapamil [Molento et al., 2004] and fexofenadine [Olsen et al., 2006].

There is an obvious lack of clinical data to be able to ascertain the risk of clinically significant drug interactions with ivermectin. Therefore, it can be debated whether it is reasonable and/or fair to administer or contradict ivermectin with drugs that are metabolized by CYP3A4 and can induce or inhibit P-glycoproteins.

VI. DISCUSSION

The present extensive review of adverse events reportedly associated with ivermectin treatment for therapeutic or prophylactic purpose did not reveal any significant cause for concern. Indeed, with the notable exception of patients with parasitic diseases such as Onchocerciasis or Loa-Loa microfiliaris, serious adverse events temporarily associated with ivermectin were very infrequent. In fact, adverse events were mainly mild to moderate and infrequent. This is confirmed by results reported in patients with scabies or human beings without any ongoing parasitic disease.

A major difficulty when tackling such an analysis of published data is to achieve a conclusive distinction between those adverse events that are temporarily associated with ivermectin treatment but presumably related to another cause, in particular an ongoing parasitic disease, and those that are presumably induced by ivermectin. Such a distinction cannot be attained in many instances.

Another difficulty of this analysis is that the vast literature on ivermectin-associated adverse events only seldom benefited from the use of causal assessment methods [reviewed in Agbabiaka et al., 2008]. Even though this is not at all a feature specific of ivermectin, this is undoubtedly a hurdle or an uncertainty factor that has to be carefully taken into consideration. It is important to keep in mind that authors may honestly, but erroneously conclude pro or con the causative role of the ivermectin treatment. Reconsidering their conclusion can be deemed to be necessary and several instances can be found in the present report.

Finally, although a strict adherence to methodological guidances is absolutely required to ensure the results of clinical trials and their statistical significance can be undisputable, the situation is different when adverse events are concerned. Clinical trials can be instrumental to precisely quantify their incidence, but this is not attainable for rare adverse events that are commonly severe. Only a case-by-case approach based on a strict medical evaluation of the causal relationship may be used. Accordingly, the results of investigative and not randomized or controlled human studies can provide useful safety information and should not be discarded.

VII. CONCLUSION

Hundreds of millions of human subjects have been treated with ivermectin for curative or prophylactic purposes worldwide over the last 3 decades. The reference list of this report demonstrates that a large body of data is available, which allows for a detailed analysis of ivermectin medical safety. Undoubtedly, uncertainties remain regarding ivermectin pharmacological effects and mechanisms of action, but when removed, this is not anticipated to alter the main conclusions of this report in any significant way as they rely on an extensive and consistent body of medical publications.

Taking into account all the above, the author of the present analysis of the available medical data concludes that the safety profile of ivermectin has so far been excellent in the majority of treated human patients so that ivermectin human toxicity cannot be claimed to be a serious cause for concern.

March 3rd, 2021

Jacques Descotes

VIII. REFERENCES

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X. AUTHOR's RESUME

1. EDUCATION

1976 M.D., cum laude, Claude Bernard University, Lyon, France
1980 Pharm.D., cum laude, Claude Bernard University
1988 Ph.D., cum laude, Claude Bernard University

2. PRESENT EMPLOYMENT

Independent Consultant (*ImmunoSafe Consultancy*): regulatory toxicity evaluation, non-clinical and clinical safety assessment (pre- and post-marketing) with special reference to the immunological safety of medicinal products, biologicals, nanomedicines and medical devices

3. PAST EMPLOYMENT

Professor of Pharmacology, Lyon-Est School of Medicine, Claude Bernard University of Lyon, and Chairman, Poison Center and Pharmacovigilance Department, Lyon University Hospitals

4. OTHER DEGREES, AFFILIATIONS AND AWARDS

1976 Diploma of Medical Toxicology, Claude Bernard University, Lyon
1977 Diploma of Cardiovascular and Renal Pharmacology, Claude Bernard University
1978 Diploma of General Pharmacology, Claude Bernard University
1978 Diploma of Biostatistics in Clinical Trials, Paris-VI University
1978 Diploma of Immunopharmacology and Immunotoxicology, Claude Bernard University
1983 Registered Expert in Pharmaco-toxicology, French Ministry of Health
1998 Eurotox Registered Toxicologist, British Toxicology Society
2001 Fellow, US Academy of Toxicological Sciences
2002 Gerhard Zbinden Annual Memorial Award, Eurotox
2010 Jeff Vos Career Achievement Award in Immunotoxicology, US Society of Toxicology
2011 Best Scientific Paper Award, American College of Toxicology
2014 Professor Emeritus, Lyon-Est School of Medicine, Claude Bernard University of Lyon

5. SCIENTIFIC OR PROFESSIONAL SOCIETIES

Committees

1986-1998 International Collaborative Immunotoxicity Study (ICICIS), IPCS/WHO & CEE
1988-1996 Program "Poison Centers in the World" (INTOX), IPCS/WHO
1992-2007 High Council for Public Hygiene, French Ministry of Health
1992-2019 Founder and President of Summerschool in Immunotoxicology
1993-2002 National Committee for the Evaluation of Pesticides, French Ministry of Agriculture
1995-Present French Expert to OECD for General Toxicology and Immunotoxicology
1997-2000 Scientific Committee on Medicinal Products and Medical Devices, DG XXIV, Commission of the European Communities, Brussels
2001-2003 Specialized Scientific Committee, French Agency for Food Safety
2001-2003 Scientific Committee on Food Safety, ILSI Europe
2003-2011 National Committee on Addicting Substances and Psychotropic Drugs, French Agency for Health Products Safety
2004-2006 National Committee on Cosmetics, French Agency for Health Products Safety
2004-2006 Committee on the Evaluation of Chemical Risks to Human Health, French Agency for Occupational and Environmental Health Safety
2004-2011 EU Risk Management Specialized Expert, CHMP, EMA
2005-2010 Rapporteur, National Committee of Biomedical Research on New Drugs, French Agency for Health Products Safety

2009-2011 Scientific Expert Committee on REACH, French Agency for Occupational and Environmental Health Safety
2009- Present Immunotoxicology (Immune Safety) Committee (HESI, Washington DC)

Editorial Committee

1988-1993 Immunopharmacology and Immunotoxicology (Marcel Dekker), Associate Editor
1993-2004 Toxicology (Elsevier, Amsterdam), Associate Editor for Immunotoxicology
1998- Present Journal of Applied Toxicology (John Wiley & sons), Editorial Board
2001-2004 Human and Experimental Toxicology (Arnold), Editorial Board
2005- Present Toxicology (Elsevier, Amsterdam), Editorial Board
2005-2011 International Immunopharmacology (Elsevier), Editorial Board
2008- Present Health Sciences (Hungarian Hygiene Society), Editorial Board
2008-2015 Open Journal of Immunology (Bentham), Editorial Board
2011-2016 Therapeutic Advances in Drug Safety (Sage Publications, London), Editorial Board
2013- Present Journal of Immunotoxicology (Taylor & Francis, New York), Editorial Board

6. SCIENTIFIC PUBLICATIONS

Books

J Descotes. *Immunotoxicology of Drugs and Chemicals*. Elsevier, Amsterdam. 1st edition (1986) and 2nd revised and updated edition (1988)
J Descotes. *Drug-Induced Immune Diseases*. Elsevier, Amsterdam, 1990
J Descotes. *Introduction à l'Immunotoxicologie*. Ed. Lacassagne, Lyon, 1992
J Descotes, F Testud, P Frantz. *Les urgences en toxicologie* (Emergencies in Toxicology). Maloine, Paris, 1992
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JH Dean, J Descotes et al. *Principles and Methods for Assessing Direct Immunotoxicity associated with Exposure to Chemicals*. Environmental Health Criteria, Vol. 180, WHO, Geneva, 1996
J Descotes. *An Introduction to Immunotoxicology*. Taylor & Francis, London, 1998
L Manzo, J Descotes, J. Hoskins. *Volatile Organic Compounds in the Environment, Risk Assessment and Neurotoxicity*. Pavia University Press, 1998
G Chevrel, JM Granvogel, H Mathieu, C Piéron, J Descotes. *Dictionnaire Pratique des Médicaments Injectables* (Practical Dictionary of Injectable Pharmaceuticals) Ed. MMI, Paris, 2001.
J Seiler, G Bode, KS Gamaniel, D Diallo, K Olejniczak, J Descotes et al. *Handbook of Non-Clinical Safety Testing*. WHO, Geneva, 2004
J Descotes. *Immunotoxicology of Drugs and Chemicals: An Experimental and Clinical Approach*. *Principles and Methods of Immunotoxicology*. Elsevier, Amsterdam, 2004
J Cohen-Tervaert, C Colosio, G Cooper, E Corsini, J Damoiseaux, J. Descotes, et al. *Principles and Methods for Assessing Autoimmunity associated with Exposure to Chemicals.* Environmental Health Criteria, Vol. 236. WHO, Geneva, 2006
RV House, J Descotes. *Cytokines in Human Health: Immunotoxicology, Pathology and Therapeutic applications*. Humana Press, Totowa, NJ, 2007
J Descotes: *Immunological Safety of Human Therapeutics and Chemicals*. Springer, Berlin (due early 2022)
J Descotes: *Immunotoxicology of Nanomedicines. A Drug Development Perspective.* Jenny Stanford Publishing, Singapore (due early 2022)

Other Publications (Index H = 42)

82 chapters in multi-authored books, 249 original scientific papers and 74 review papers in peer-reviewed journals, 486 presentations and posters at scientific meetings on the preclinical and medical safety assessment, immunotoxicology and immunological safety, regulatory safety and risk evaluation of medicinal products and chemicals.